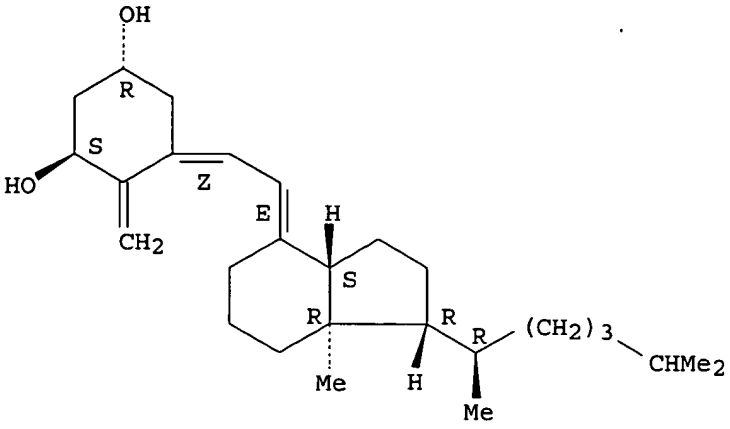

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1060 REFERENCES IN FILE CA (1967 TO DATE)
23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1060 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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=> fil reg
FILE 'REGISTRY' ENTERED AT 13:27:32 ON 16 SEP 2001
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DICTIONARY FILE UPDATES:  14 SEP 2001  HIGHEST RN 357154-15-5

TSCA INFORMATION NOW CURRENT THROUGH January 11, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

=> d sta que l34
L32             STR
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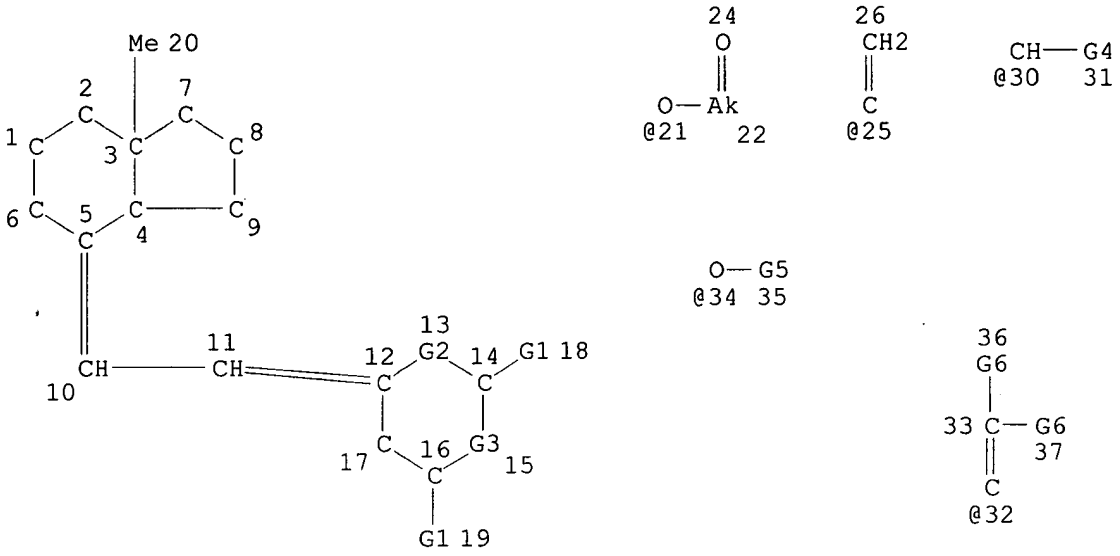


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VAR G2=CH2/25
VAR G3=CH2/30/32
VAR G4=34/CY/AK
VAR G5=AK/CY
VAR G6=H/AK/CY
NODE ATTRIBUTES:
CONNECT IS M1  RC AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  12   5
NUMBER OF NODES IS  33

STEREO ATTRIBUTES: NONE
L34        2873 SEA FILE=REGISTRY CSS FUL L32

100.0% PROCESSED   7433 ITERATIONS                    2873 ANSWERS
SEARCH TIME: 00.00.03


=> d his
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               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 12:39:20 ON 16 SEP 2001
               E DELUCA H/AU
L1          1095 S E3,E6,E7,E9,E10
               E MCCARY L/AU
L2             4 S E4,E5
               E MC CARY L/AU
               E ZELLA J/AU

     FILE 'REGISTRY' ENTERED AT 12:41:53 ON 16 SEP 2001
L3             1 S 1406-16-2

     FILE 'HCAPLUS' ENTERED AT 12:41:58 ON 16 SEP 2001
L4          6051 S L3
L5           253 S L1,L2 AND L4
L6           845 S L1,L2 AND VITAMIN(L)D#
L7            94 S L1,L2 AND VITAMIN(L)D2
L8           548 S L1,L2 AND VITAMIN(L)D3
L9         16799 S VITAMIN D
L10         2247 S 1 ALPHA 25 DIHYDROXYVITAMIN D3
L11           52 S 1 ALPHA HYDROXY VITAMIN D3
L12          630 S 1 ALPHA HYDROXYVITAMIN D3
L13           65 S 1()ALPHA()(HYDROXYVITAMIN OR HYDROXY VITAMIN)()D2
L14            0 S 19 NOR 1 25 DIHYDROXY 21 EPI VITAMIN D3
L15            0 S 19 NOR 1 25 DIHYDROXY 21 EPIVITAMIN D3
L16            1 S 19(L)NOR(L)DIHYDROXY(L)(EPIVITAMIN OR EPI(L)VITAMIN)(L)D3
L17            0 S 1 25 DIHYDROXY (L) DEHYDRO (L) 24 (L) HOMOVITAMIN(L)D3
L18            0 S 1 25 DIHYDROXY (L) DEHYDRO (L) 24 (L) HOMO (L) VITAMIN(L)D3
L19            1 S DIHYDROXY (L) DEHYDRO (L) HOMO (L) VITAMIN(L)D3
L20         3079 S 1 25 OH 2D3
L21            0 S 19 NOR 1 25 OH 2D3
L22            0 S 22E 1 25 OH 2D3
L23            1 S 1 25 OH 2 24 HOMO D3

     FILE 'REGISTRY' ENTERED AT 12:52:50 ON 16 SEP 2001
L24            3 S 32222-06-3 OR 41294-56-8 OR 54573-75-0

     FILE 'HCAPLUS' ENTERED AT 12:53:30 ON 16 SEP 2001
L25         9243 S L24
L26          341 S L1,L2 AND L25
L27          911 S L5-L8,L26
L28          201 S L1,L2 AND L10-L23
L29          915 S L27,L28

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     FILE 'HCAPLUS' ENTERED AT 12:54:35 ON 16 SEP 2001
               SET SMARTSELECT ON
L30           SEL L29 1- RN :    2009 TERMS
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     FILE 'REGISTRY' ENTERED AT 12:55:00 ON 16 SEP 2001
L31         2001 S L30
L32               STR
L33           50 S L32 CSS
L34         2873 S L32 CSS FUL
               SAV L34 KARL769/A
L35          325 S L34 AND L31
L36         2874 S L3,L24,L35,L34
L37            2 S GLUCOSE/CN
L38            1 S INSULIN/CN

     FILE 'HCAPLUS' ENTERED AT 13:06:11 ON 16 SEP 2001
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L39       15848 S L36
                E DIABET/CW
L40       43215 S E4,E5
                E ANTIDIABET/CW
L41        8717 S E4,E5
                E DIBIABET/CT
                E DIABET/CT
                E E4+ALL
L42        1984 S E1
                E E2+ALL
L43        1149 S E2+NT
                E DIBIABET/CT
                E DIABET/CT
                E E4+ALL
                E E3+ALL
L44       39552 S E4+NT
                E E11+ALL
L45        4246 S E2,E3
                E E16+ALL
L46        5435 S E2
L47         176 S L39 AND L40-L46
L48         165 S L39 AND L37
L49         202 S L39 AND L38
L50         449 S L47-L49
                E BLOOD GLUCOSE/CT
                E E3+ALL
L51       10188 S E1
L52        7915 S E2
L53          20 S L39 AND L51,L52
                E INSULIN/CT
                E E3+ALL
L54        9092 S E6,E8-E10
L55       11935 S E14
L56        4309 S E13+NT
L57          24 S L39 AND L54-L56
L58         460 S L50,L53,L57
L59          93 S L36 (L) THU/RL AND L58
L60           4 S L1,L2 AND L58
                E PANCREATIC ISLET/CT
                E E21+ALL
L61          57 S L39 AND E11,E12,E10+NT
L62          52 S L39 AND E9
L63         518 S L58,L61,L62
L64           6 S L1,L2 AND L63
L65         102 S L36 (L) THU/RL AND L63
L66         102 S L59,L65
L67          33 S L66 AND ?DIABET?(L)MELLITUS
L68           6 S L66 AND ?DIABET?(L) TYPE I
L69           3 S L66 AND ?DIABET?(L) TYPE 1
L70          17 S L66 AND ?DIABET?(L) ?INSULIN?
L71          37 S L67-L70
L72       11100 S L34
L73          54 S L72 AND L66
L74          27 S L73 AND L71
L75          25 S L74 NOT UPDATE/TI
L76          27 S L73 NOT L74
L77          11 S L76 AND (ANALOG# OR DIABET? OR RXR OR ISLET OR UREMI#)/TI
L78           8 S L77 NOT (RETINOID OR BREAST OR HYPERCALCEMIA)/TI
L79          39 S L64,L75,L78
L80          17 S L24 AND L79
L81          39 S L79,L80

     FILE 'REGISTRY' ENTERED AT 13:27:32 ON 16 SEP 2001

=> fil hcaplus
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FILE COVERS 1947 - 16 Sep 2001 VOL 135 ISS 13
FILE LAST UPDATED: 14 Sep 2001 (20010914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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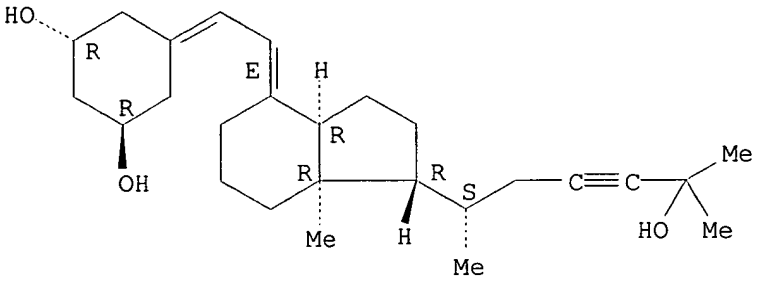
=> d all tot l81 fhitstr

L81 ANSWER 1 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:374037 HCAPLUS
TI Immunomodulatory properties of a 1,25(OH)2 vitamin D3 **analog** combined with IFN.beta. in an animal model of syngeneic **islet** transplantation
AU van Etten, E.; Gysemans, C.; Verstuyf, A.; Bouillon, R.; Mathieu, C.
CS Laboratory of Experimental Medicine and Endocrinology, Katholieke Universiteit Leuven, Louvain, Belg.
SO Transplant. Proc. (2001), 33(3), 2319
CODEN: TRPPA8; ISSN: 0041-1345
PB Elsevier Science Inc.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 1, 15
AB Immunomodulation obtained by combinations of TX527 (vitamin D3 analog), with interferon-.beta. (IFN.beta.) and cyclosporin A (CyA) in syngeneic islet transplantation in spontaneously diabetic NOD mice was evaluated. All control mice showed disease recurrence within 2 wk after transplantation. The islet graft survival was not (TX527 and IFN.beta.) or only slightly (CyA) prolonged by monotherapies. Combination of TX527 with CyA and with IFN.beta. prolonged syngeneic graft survival.
ST TX527 interferon beta cyclosporin immunomodulation transplant
IT Immunomodulators
(immunomodulation by TX527 with cyclosporin A and IFN.beta. in syngeneic islet transplantation)
IT Transplant and Transplantation
(pancreatic islet; immunomodulation by TX527 with cyclosporin A and IFN.beta. in syngeneic islet transplantation)
IT Drug interactions
(synergistic; immunomodulation by TX527 with cyclosporin A and IFN.beta. in syngeneic islet transplantation)
IT **Pancreatic islet of Langerhans**
(transplant; immunomodulation by TX527 with cyclosporin A and IFN.beta. in syngeneic islet transplantation)
IT Interferons
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(.beta.; immunomodulation by TX527 with cyclosporin A and IFN.beta. in syngeneic islet transplantation)
IT 59865-13-3, Cyclosporin A **163379-89-3**, TX527
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(immunomodulation by TX527 with cyclosporin A and IFN.beta. in syngeneic islet transplantation)
RE.CNT 2
RE
(1) Van Etten, E; Transplantation 2000, V69, P1932 HCAPLUS
(2) Yong, W; Neurology 1998, V51, P682
IT **163379-89-3**, TX527
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(immunomodulation by TX527 with cyclosporin A and IFN.beta. in syngeneic islet transplantation)
RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1.alpha.,3.beta.,7E,14.beta.,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 2 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:272961 HCAPLUS
DN 134:321240
TI Beneficial effect of 1,25 dihydroxyvitamin D3 on cytokine-treated human pancreatic islets
AU Riachy, R.; Vandewalle, B.; Belaich, S.; Kerr-Conte, J.; Gmyr, V.; Zerimech, F.; D'Herbomez, M.; Lefebvre, J.; Pattou, F.
CS Laboratoire d'Endocrinologie Experimentale, UPRES 1048, Faculte de Medecine, Lille, 59045, Fr.
SO J. Endocrinol. (2001), 169(1), 161-168
CODEN: JOENAK; ISSN: 0022-0795
PB Society for Endocrinology
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 15
AB We examd. whether 1,25 dihydroxyvitamin D3 (1,25 D3), the active form of vitamin D involved in the regulation of the immune system, may also protect human pancreatic islet cells from destruction induced by cytokines. In this study, we specifically investigated the effect of 1,25 D3 on oxidative stress and major histocompatibility complex (MHC) induction, both implicated in cytokine-induced islet cell dysfunction and destruction. We also investigated the effects of 1,25 D3 on interleukin (IL)-6, a pleiotropic cytokine implicated in the pathogenesis of immunoinflammatory disorders. Human pancreatic islets, isolated from heart-beating donors, were treated with a combination of three cytokines, IL-1.beta. + tumor necrosis factor .alpha. + interferon .gamma., in the presence or absence of vitamin D, and compared with untreated control cells. Metabolic activity was assessed by cell viability and **insulin** content. Oxidative stress was estd. by heat shock protein

70 (hsp70) expression, cell manganese superoxide dismutase (MnSOD) activity and nitrite release, a reflexion of nitric oxide (NO) synthesis. Variation of immunogenicity of islet prepns. was detd. by anal. of the MHC class I and class II transcripts. Inflammatory status was evaluated by IL-6 prodn. After 48 h of contact with cytokines, **insulin** content was significantly decreased by 40% but cell viability was not altered. MHC expression significantly increased six- to sevenfold as well as NO and IL-6 release (two- to threefold enhancement). MnSOD activity was not significantly induced and hsp70 expression was not affected by the combination of cytokines. The addn. of 1,25 D3 significantly reduced nitrite release, IL-6 prodn. and MHC class I expression which then became not significantly different from controls. These results suggest that the effect of 1,25 D3 in human pancreatic islets cells may be a redn. of the vulnerability of cells to cytotoxic T lymphocytes and a redn. of cytotoxic challenge. Hence, 1,25 D3 might play a role in the prevention of **type 1 diabetes** and islet allograft rejection.

ST dihydroxyvitamin D3 cytokine pancreatic islet

IT Heat-shock proteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(HSP 70; dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT Histocompatibility antigens
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(MHC (major histocompatibility complex), class I; dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT Histocompatibility antigens
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(MHC (major histocompatibility complex), class II; dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT Oxidative stress, biological
Pancreatic islet of Langerhans
(dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT Interleukin 1.beta.
Tumor necrosis factors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT Interleukin 6
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT Interferons
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(.gamma.; dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT **32222-06-3**, 1.alpha.,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT **9004-10-8**, Insulin, biological studies 9054-89-1, Superoxide dismutase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

IT 10102-43-9, Nitric oxide, biological studies 14797-65-0, Nitrite, biological studies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)

RE.CNT 54

RE

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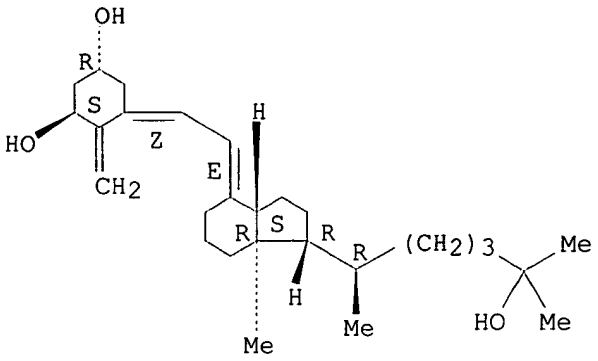
IT **32222-06-3**, 1.alpha.,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 beneficial effect on cytokine-treated human pancreatic islets)
RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 3 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:248768 HCAPLUS
DN 135:755
TI 1.alpha., 25-Dihydroxyvitamin D3 suppresses the effect of streptozotocin-induced diabetes during chemical rat liver carcinogenesis
AU Saha, Barun Kanti; Sarkar, Alok; Basak, Ranjan; Chatterjee, Malay
CS Division of Biochemistry, Department of Pharmaceutical Technology, Jadavpur University, Calcutta, 700 032, India
SO Cell Biol. Int. (2001), 25(3), 227-237
CODEN: CBIIEV; ISSN: 1065-6995
PB Academic Press
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The effect of streptozotocin-induced diabetes in male Sprague-Dawley rats was investigated to ascertain whether it has had any modulating role in hepatocarcinogenesis. Hepatocarcinogenesis was initiated with a single sub-necrogenic dose of diethylnitrosamine (DEN) (125 mg/kg body wt., i.p.) while acute diabetes was produced with a single i.p. injection of streptozotocin (STZ) (65 mg/kg body wt.). STZ was administered either before or after initiation with DEN at 3-wk intervals. With this basic exptl. regimen, the effect of an antioxidant vitamin, 1.alpha., 25-dihydroxyvitamin D3(VD) (0.3 .mu.g/ 0.1 mL propylene glycol per os twice a week), was investigated with effect from 4 wk prior to the exposure of DEN or STZ. Primary routine histopathol., hepatic nodular morphometric anal. and major preneoplastic antioxidant and drug metabolizing enzymes were tested either with or without VD treatment in different exptl. and control groups. Observation of the hepatic nodulogenesis, pathol. and level of the antioxidant and drug metabolizing enzyme pattern of the tissue showed a marked protection in different exptl. groups of rats treated with VD. It may be that VD could elicit an anticarcinogenic potential in the aforesaid regimen by resetting the effects of these biomarkers induced by DEN and/or STZ. The authors further propose that STZ, when administered 3 wk after DEN, caused massive damage where its action in vivo could be comparable with any known promoter that could propel the process of carcinogenesis more efficiently than when it was applied before the carcinogen. (c) 2001 Academic Press.
ST dihydroxyvitamin D3 chemoprevention diabetes liver carcinogenesis rat

IT Antitumor agents
Diabetes mellitus
Liver, neoplasm
Transformation, neoplastic
(1.alpha., 25-dihydroxyvitamin D3 suppresses effect of streptozotocin-induced **diabetes** during chem. rat liver carcinogenesis)
IT Peroxidation
(lipid; 1.alpha., 25-dihydroxyvitamin D3 suppresses effect of streptozotocin-induced diabetes during chem. rat liver carcinogenesis)
IT 55-18-5, Diethylnitrosamine 18883-66-4, Streptozotocin
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(1.alpha., 25-dihydroxyvitamin D3 suppresses effect of streptozotocin-induced diabetes during chem. rat liver carcinogenesis)
IT **32222-06-3**, 1.alpha., 25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(1.alpha., 25-dihydroxyvitamin D3 suppresses effect of streptozotocin-induced diabetes during chem. rat liver carcinogenesis)
IT 70-18-8, Reduced glutathione, biological studies 9035-51-2, Cytochrome P450, biological studies 9046-27-9, .gamma.-Glutamyltranspeptidase 50812-37-8, Glutathione S-transferase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(1.alpha., 25-dihydroxyvitamin D3 suppresses effect of streptozotocin-induced diabetes during chem. rat liver carcinogenesis)
IT 542-78-9, Malondialdehyde
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(1.alpha., 25-dihydroxyvitamin D3 suppresses effect of streptozotocin-induced diabetes during chem. rat liver carcinogenesis)
IT **50-99-7**, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**blood**; 1.alpha., 25-dihydroxyvitamin D3 suppresses effect of streptozotocin-induced diabetes during chem. rat liver carcinogenesis)
RE.CNT 44
RE
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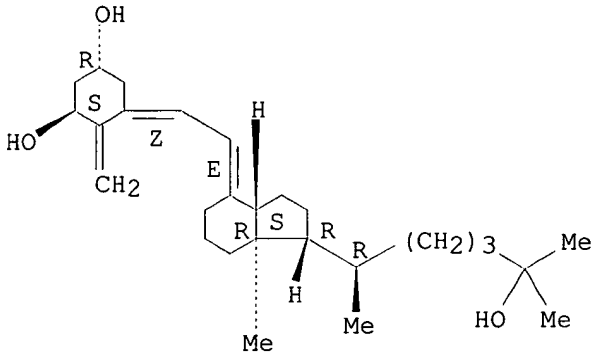
IT **32222-06-3**, 1.alpha., 25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(1.alpha., 25-dihydroxyvitamin D3 suppresses effect of streptozotocin-induced diabetes during chem. rat liver carcinogenesis)
RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

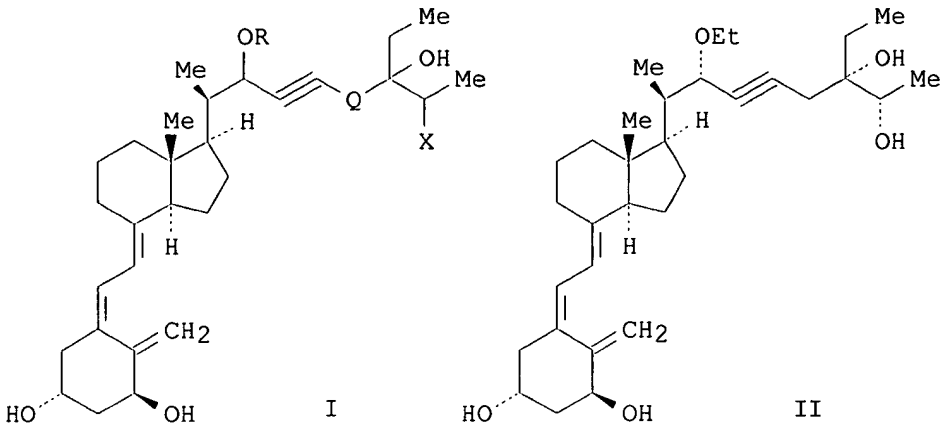


L81 ANSWER 4 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:115113 HCAPLUS
DN 134:163204
TI Synthesis of novel vitamin D analogues as pharmaceutical agents
IN Bretting, Claus Aage Svensgaard
PA Leo Pharmaceutical Products Ltd. A/S (Lovens Kemiske Fabrik Produktionsaktie, Den.
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59
CC 32-7 (Steroids)
Section cross-reference(s): 1, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001010829	A1	20010215	WO 2000-DK389	20000711

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,

AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 1999-147200 P 19990804
OS MARPAT 134:163204
GI



AB Vitamin D analogs of formula I [R = H, alkyl, Ph, aralkyl, etc.; Q = (CH2)n; n = 0-2; X = OH, halogen] are prepd. These compds. have been discovered to possess strong activity in inducing differentiation and inhibiting undesirable proliferation of certain cells as well as immunomodulating and anti-inflammatory effects (no data). Thus, II was prepd. in several steps from secopregnatrienecarboxaldehyde deriv. A capsule and a dermatol. cream contg. I is also described.

ST vitamin D analog prepn anticancer antiinflammatory immunomodulator

IT Skin, disease
(atrophy; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of steroid induced skin atrophy)

IT Isomerization
(cis-trans, photochem.; prepn. of novel vitamin D analogs as pharmaceutical agents)

IT Nervous system
(degeneration; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of neurodegenerative diseases)

IT Brain, neoplasm
(glial; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of brain cancer)

IT Transplant and Transplantation
(graft-vs.-host reaction; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of graft-vs.-host reaction)

IT Transplant and Transplantation
(host-vs.-graft reaction; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of host-vs.-graft reaction)

IT Skin
(keratinization; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of disturbances of keratinization)

IT Antitumor agents
(leukemia; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of leukemia)

IT Myeloproliferative disorders
(myelofibrosis; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of myelofibrosis)

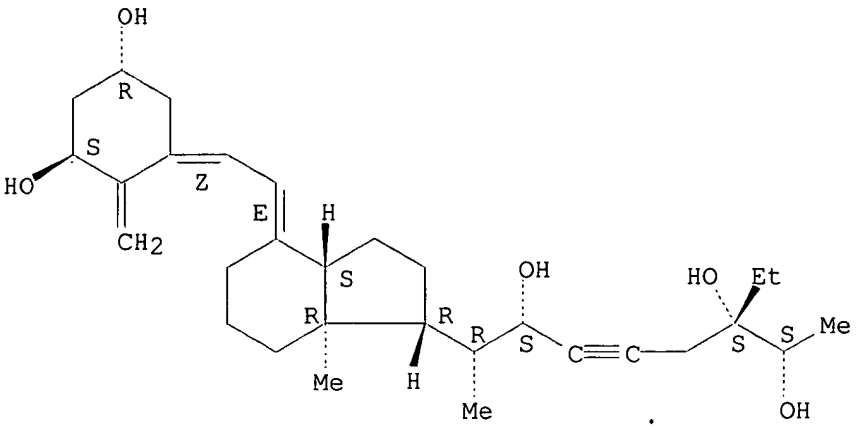
IT Mammary gland
(neoplasm; prepn. of novel vitamin D analogs as pharmaceutical agents

for the treatment of mammary cancer)
IT Bone, neoplasm
(osteosarcoma; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of osteosarcoma)
IT Skin, disease
(pemphigus vulgaris; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of pemphigus vulgaris)
IT Anti-inflammatory agents
(prepn. of novel vitamin D analogs as anti-inflammatory drugs)
IT Immunomodulators
(prepn. of novel vitamin D analogs as immunomodulators)
IT Antitumor agents
(prepn. of novel vitamin D analogs as pharmaceutical agents)
IT Vitamins
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel vitamin D analogs as pharmaceutical agents)
IT Bone formation
(prepn. of novel vitamin D analogs as pharmaceutical agents for promoting osteogenesis)
IT Alzheimer's disease
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of Alzheimer's senile dementia)
IT Human immunodeficiency virus
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of HIV-assocd. dermatoses)
IT Acne
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of acne)
IT Alopecia
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of alopecia)
IT Autoimmune disease
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of autoimmune diseases including discoid and chronic dermatoses of autoimmune type)
IT **Diabetes mellitus**
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of **diabetes mellitus**)
IT Immune system
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of diseases of, or imbalances in, the immune system)
IT Hypertension
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of hypertension)
IT Asthma
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of inflammatory diseases, such as asthma)
IT Rheumatoid arthritis
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of inflammatory diseases, such as rheumatoid arthritis)
IT Melanoma
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of melanoma)
IT Psoriasis
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of psoriasis including pustulosis palmoplantaris, acrodermatitis continua and nail psoriasis)
IT Aging, animal
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of skin ageing including photo ageing)
IT Skin, neoplasm
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of skin cancer)
IT Transplant rejection

(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of treatment of transplant rejection)
IT Wound healing
(prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of wound healing)
IT Osteomalacia
(prepn. of novel vitamin D analogs as pharmaceutical agents for treating or preventing osteomalacia)
IT Osteoporosis
(prepn. of novel vitamin D analogs as pharmaceutical agents for treating or preventing osteoporosis)
IT Etherification
(prepn. of novel vitamin D analogs as pharmaceutical agents via alkylation at the 22-hydroxy group with alkyl or aralkyl bromide or iodide in the presence of a base and a phase transfer catalyst)
IT Connective tissue
(scleroderma; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of scleroderma)
IT Hyperparathyroidism
(secondary; prepn. of novel vitamin D analogs as pharmaceutical agents for treatment of secondary hyperparathyroidism assocd. with renal failure)
IT Lupus erythematosus
(systemic; prepn. of novel vitamin D analogs as pharmaceutical agents for the treatment of systemic lupus erythematosus)
IT **325689-36-9P 325689-37-0P 325689-38-1P**
325689-39-2P 325689-40-5P 325689-41-6P
325689-42-7P 325689-43-8P 325689-44-9P
325689-45-0P 325689-47-2P 325689-48-3P
325689-49-4P 325689-50-7P 325689-51-8P
325689-52-9P 325689-53-0P 325689-54-1P
325689-61-0P 325689-74-5P 325689-83-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel vitamin D analogs as pharmaceutical agents)
IT 74-88-4, Methyl iodide, reactions 74-96-4, Ethyl bromide 75-77-4, Trimethylchlorosilane, reactions 77-76-9, 2,2-Dimethoxypropane 100-39-0, Benzyl bromide 106-94-5, Propyl bromide 106-96-7, Propargyl bromide 116-11-0 124-63-0, Methane sulfonyl chloride 349-43-9, Ethyl 2-fluoropropionate 687-47-8, Ethyl (-)-lactate 925-90-6, Ethyl magnesium bromide 1066-54-2, Trimethylsilylacetylene 1111-64-4, Lithium acetylide 2366-56-5, Methyl 2-fluoropropionate 7699-00-5, (+)-Ethyl lactate 17392-83-5, Methyl (+)-lactate 18162-48-6, tert-Butyl dimethylsilylchloride 18295-60-8, Allenylmagnesium bromide 106513-42-2 115648-67-4 325689-84-7
RL: RCT (Reactant)
(prepn. of novel vitamin D analogs as pharmaceutical agents)
IT 146805-74-5P 169904-58-9P 187590-50-7P 325689-55-2P 325689-56-3P
325689-57-4P 325689-58-5P 325689-59-6P 325689-60-9P 325689-62-1P
325689-63-2P 325689-64-3P 325689-65-4P 325689-66-5P 325689-67-6P
325689-68-7P 325689-69-8P 325689-70-1P 325689-71-2P 325689-72-3P
325689-73-4P 325689-75-6P 325689-77-8P 325689-79-0P 325689-81-4P
325689-82-5P 325689-85-8P 325689-86-9P 325689-87-0P 325689-88-1P
325689-89-2P 325689-90-5P 325689-91-6P 325689-92-7P 325689-93-8P
325689-94-9P 325689-95-0P 325689-96-1P 325689-97-2P 325689-98-3P
325689-99-4P 325690-00-4P 325690-01-5P 325690-02-6P 325690-03-7P
325690-04-8P 325690-05-9P 325690-06-0P 325690-07-1P 325690-08-2P
325690-09-3P 325690-10-6P 325690-11-7P 325690-12-8P 325690-13-9P
325690-14-0P 325690-15-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of novel vitamin D analogs as pharmaceutical agents)
RE.CNT 1
RE
(1) Leo Pharmaceutical Products Ltd AS; WO 9319044 A1 1993 HCAPLUS
IT **325689-36-9P**

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel vitamin D analogs as pharmaceutical agents)
RN 325689-36-9 HCAPLUS
CN 5-Nonyne-2,3,7-triol, 8-[(1R,3aS,4E,7aR)-4-[(2Z)-[(3S,5R)-3,5-dihydroxy-2-methylenecyclohexylidene]ethylidene]octahydro-7a-methyl-1H-inden-1-yl]-3-ethyl-, (2S,3S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 5 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:78357 HCAPLUS
DN 134:131708
TI Preparation and bioactivity of vitamin D derivs. with cyclic substructures in the side chains
IN Steinmeyer, Andreas; Schwarz, Katica; Giesen, Claudia; Haberey, Martin; Fahnrich, Marianne
PA Schering Aktiengsellschaft, Germany
SO PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM C07C401-00
CC 32-7 (Steroids)
Section cross-reference(s): 1, 2, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001007405	A2	20010201	WO 2000-EP7104	20000724
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19935771	A1	20010201	DE 1999-19935771	19990723
PRAI DE 1999-19935771	A	19990723		

OS MARPAT 134:131708
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention describes the synthesis of vitamin D derivs. [I; Y1, Y2 = OH, alkanoyloxy, aroyloxy; R1, R2 = H; R1R2 = CH2; R3, R4 = H, Cl, F, alkyl, etc.; Q = alkylene chain; X1, X2 = H, OH, Cl, F, Br, etc.; Z = (un)substituted, (un)satd. or arom. 5-, 6-membered carbo-, heterocyclic ring], the intermediates used in the process, and the prodn. of medicaments. Thus, vitamin D analog II was prepd. via Wittig reaction of ketone III (also prepd.) with IV, followed by deprotection. II had competition factor of 5 vs. calcitriol towards receptor binding and dose relation for differentiation induction in HL 60 cell.

ST vitamin D carbocyclic heterocyclic analog prepn; receptor vitamin D analog prepn

IT Oxidation
(Collins; prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT Cell differentiation
(HL 60; prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT Oxidation
(Swern; prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-CD4; in combination with vitamin D derivs. with cyclic substructures in the side chains for their use in medicaments)

IT Skin, disease
(hyperproliferation; prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT **Diabetes mellitus**
(**insulin**-dependent; prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT AIDS (disease)
Antitumor agents
Asthma
Eczema
Lupus erythematosus
Myasthenia gravis
Osteoporosis
Psoriasis
Rheumatoid arthritis
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT 9,10-Secosteroids
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT Vitamin D receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT Wittig reaction
(stereoselective; between phosphonate and ketone in prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hypercalcemia; prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT 53123-88-9, Rapamycin 59865-13-3, Cyclosporin A 104987-11-3, FK 506
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with vitamin D derivs. with cyclic substructures in the side chains for their use in medicaments)

IT 178424-15-2P **321909-29-9P 321909-32-4P**
321909-39-1P 321909-41-5P 321909-44-8P
321909-46-0P 321909-53-9P 321909-58-4P
321909-60-8P 321909-67-5P 321909-69-7P
321909-72-2P 321909-79-9P 321909-81-3P
321909-87-9P 321909-91-5P 321910-05-8P
321910-19-4P 321910-21-8P 321910-28-5P
321910-30-9P 321910-40-1P 321910-42-3P
321910-49-0P 321910-51-4P 321910-58-1P
321910-60-5P 321910-67-2P 321910-71-8P
321910-78-5P 321910-80-9P 321910-87-6P
321910-89-8P 321910-97-8P 321910-99-0P
321911-10-8P 321911-12-0P 321911-15-3P
321911-17-5P 321911-20-0P 321911-22-2P
321911-24-4P 321911-26-6P 321911-28-8P
321911-30-2P 321911-32-4P 321911-34-6P
321911-40-4P 321911-42-6P 321911-43-7P
321911-45-9P 321911-63-1P 321911-64-2P
321911-65-3P 321911-66-4P 321911-67-5P
321911-68-6P 321911-69-7P 321911-70-0P
321911-71-1P 321911-72-2P 321911-73-3P
321911-74-4P 321911-75-5P 321911-76-6P
321911-77-7P 321911-78-8P 321911-79-9P
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321911-83-5P 321911-84-6P 321911-85-7P
321911-86-8P 321911-87-9P 321911-88-0P
321911-89-1P 321911-90-4P 321911-91-5P
321911-93-7P 321911-94-8P 321911-95-9P
321911-96-0P 321911-98-2P 321911-99-3P
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321912-04-3P 321912-05-4P 321912-06-5P
321912-07-6P 321912-08-7P 321912-09-8P
321912-10-1P 321912-11-2P 321912-12-3P
321912-13-4P 321912-14-5P 321912-15-6P
321912-16-7P 321912-17-8P 321912-18-9P
321939-19-9P 321939-20-2P 321939-21-3P
321939-23-5P 321939-25-7P 321939-26-8P
322397-78-4P 322397-80-8P 322397-83-1P 322397-86-4P 322397-93-3P
322399-67-7P 322399-68-8P 322399-69-9P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT 60-29-7, Diethylether, uses 108-88-3, Toluene, uses 109-99-9, Tetrahydrofuran, uses 110-54-3, Hexane, uses 123-91-1, Dioxane, uses
RL: NUU (Nonbiological use, unclassified); USES (Uses)
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT 75-05-8, Acetonitrile, reactions 87-13-8, Ethoxymethylene malonic acid diethyl ester 95-15-8, 1-Benzothiophene 95-16-9, Benzothiazole 98-59-9, p-Toluenesulfonyl chloride 98-88-4, Benzoyl chloride 104-92-7, 4-Bromo-methoxybenzene 106-38-7, 4-Bromotoluene 108-24-7, Acetic anhydride 109-72-8, Butyl lithium, reactions 110-02-1, Thiophene 110-87-2 124-63-0, Methanesulfonyl chloride 137-00-8, 5-(2-Hydroxyethyl)-4-methylthiazole 271-89-6, 2,3-Benzofuran 288-42-6, Oxazole 302-01-2, Hydrazine, reactions 402-43-7, 4-Trifluoromethylbromobenzene 616-44-4, 3-Methylthiophene 693-95-8, 4-Methylthiazole 829-85-6, Diphenylphosphine 872-55-9, 2-Ethylthiophene 994-30-9, Chlorotriethylsilane 1191-15-7, DIBAH 1632-83-3, 1-Methylbenzimidazole 2746-25-0, 4-Methoxybenzylbromide 3034-53-5, 2-Bromothiazole 6089-04-9 16853-85-3 18162-48-6, tert-Butyldimethylsilylchloride 19287-45-7, Diborane 20039-37-6

22722-98-1, RedAl 26299-14-9, Pyridinium chlorochromate 55812-82-3
57267-03-5, Triethoxy acetic acid ethyl ester 81506-41-4 81522-68-1
112924-91-1 139356-39-1 321911-92-6 322391-98-0 322399-70-2
RL: RCT (Reactant)
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT 7251-53-8P 114694-12-1P 114694-13-2P 135604-76-1P 141171-60-0P
166405-64-7P 178424-16-3P 186372-30-5P 189102-18-9P 189102-56-5P
235107-96-7P 235107-97-8P 235108-11-9P 266343-17-3P 321909-18-6P
321909-19-7P 321909-20-0P 321909-21-1P 321909-22-2P 321909-23-3P
321909-24-4P 321909-25-5P 321909-26-6P 321909-27-7P 321909-28-8P
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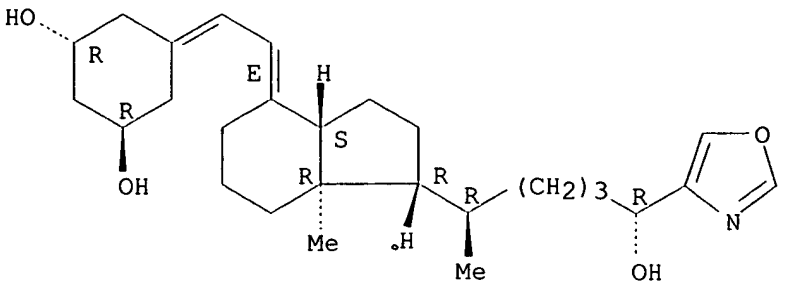
322397-84-2P 322397-89-7P 322397-91-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT **321909-55-1P** 321911-62-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

IT **321909-29-9P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and bioactivity of vitamin D derivs. with cyclic substructures in the side chains)

RN 321909-29-9 HCAPLUS
CN 19,26,27-Trinor-9,10-secocholesta-5,7-diene-1,3,25-triol, 25-(4-oxazolyl)-, (1.alpha.,3.beta.,7E,25R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 6 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:699515 HCAPLUS
DN 131:332572
TI A vitamin D3 derivative (CB1093) induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats
AU Riaz, S.; Malcangio, M.; Miller, M.; Tomlinson, D. R.
CS Department Pharmacology, Queen Mary Westfield College, London, UK
SO Diabetologia (1999), 42(11), 1308-1313
CODEN: DBTGAJ; ISSN: 0012-186X
PB Springer-Verlag
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Streptozotocin-diabetic rats show impaired neurotrophic support by deficient nerve growth factor (NGF) in muscle and skin. We, therefore, examd. a novel agent (CB1093; 1(S),3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene), which induces expression of endogenous nerve growth factor. We gave CB1093 orally followed by measurements of mech. nociception, nerve growth factor, neuropeptides (immunoassay) and nerve growth factor receptors (Western blots). In non-diabetic rats CB1093 caused dose-de-pendent increases in nerve growth factor prodn. (140% in soleus muscle and 190% in sciatic nerve) and a mech. hyperalgesia in the foot. There was also increased sciatic nerve expression of neuronal NGF target gene products, substance P (16%) and calcitonin gene-related peptide (CGRP; 52%). Nerve growth factordepletions of nerve growth factor, substance P and CGRP in sciatic nerves of diabetic rats were prevented by CB1093, which also increased soleus nerve growth factor concns. to 30% over those seen in non-diabetic rats and increased its mRNA expression in skin.nerve growth factor. The CB1093 did not affect expression of nerve growth factor receptors (trkA and p75NTR) in dorsal root ganglia in control or diabetic rats, though the p75NTR expression was reduced by diabetes. The mech. hyperalgesia seen in diabetic rats treated with vehicle was not exacerbated by CB1093. These findings show that in animal models of diabetes it is possible to prevent depletions of nerve growth factor and the products of its neuronal target genes by oral treatment of a highly potent inducer of NGF gene expression. Pain is a possible side-effect, though this was a function of dose and was manifest more in controls than in diabetic rats.
ST diabetes vitamin D3 deriv nerve growth factor; CB1093 diabetes nerve growth factor
IT **Diabetes mellitus**
(CB1093 induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-**diabetic** rats)
IT Nerve, disease
(diabetic neuropathy; CB1093 induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats)
IT **167678-65-1**
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(CB1093 induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats)
IT 9061-61-4, Nerve growth factor

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(CB1093 induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats)

RE.CNT 37

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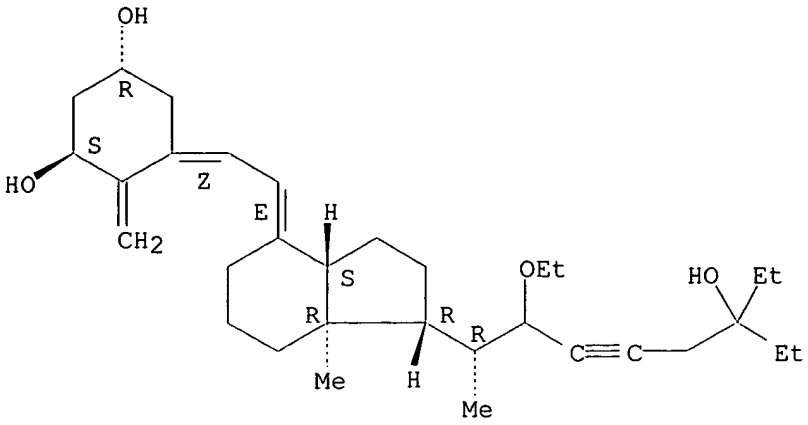
IT **167678-65-1**

RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(CB1093 induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats)

RN 167678-65-1 HCAPLUS

CN 1,3-Cyclohexanediol, 5-[(2E)-[(1R,3aS,7aR)-1-[(1R)-2-ethoxy-6-ethyl-6-hydroxy-1-methyl-3-octynyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 7 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:570650 HCAPLUS
DN 131:194774
TI Poor glycemic control impairs the response of biochemical parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in patients with type 2 diabetes
AU Inaba, M.; Nishizawa, Y.; Mita, K.; Kumeda, Y.; Emoto, M.; Kawagishi, T.; Ishimura, E.; Nakatsuka, K.; Shioi, A.; Morii, H.
CS Second Department of Internal Medicine, Osaka City University Medical School, Osaka, 545, Japan
SO Osteoporosis Int. (1999), 9(6), 525-531
CODEN: OSINEP; ISSN: 0937-941X
PB Springer-Verlag London Ltd.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Osteoblast deficit plays a principal role in the development of **diabetic** osteopenia. We have previously reported that high glucose conditions impair the function of osteoblast-like MG-63 cells. This study was performed to assess the sensitivity of osteoblasts to 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) in patients with type 2 **diabetes** without **insulin** deficiency or overt **diabetic** complications. During stimulation with 1,25(OH)2D3 at 2.0 .mu.g/day for 6 consecutive days in 9 type 2 **diabetic** patients, serum levels of bone alk. phosphatase (BALP), osteocalcin (OC) and the carboxyterminal propeptide of **type 1** procollagen, and the urinary excretion of pyridinoline and deoxypyridinoline (DPYR), were monitored. As parameters of glycemic control, the mean level of fasting plasma glucose (mFPG) throughout the 1,25(OH)2D3 stimulation test and the level of HbA1C were used. 1,25(OH)2D3 increased serum 1,25(OH)2D significantly by day 2, which was followed by a significant redn. in the serum level of intact parathyroid hormone. The maximal increment of serum OC adjusted for that of 1,25(OH)2D was neg. correlated with both mFPG and HbA1C levels ($p < 0.05$). Furthermore, the magnitude of 1,25(OH)2D3-induced bone resorption, as reflected by the maximal increase in urinary DPYR excretion, was neg. correlated with the mFPG level ($p < 0.05$). Basal BALP tended to be neg. correlated with HbA1C, although not to a significant extent. In conclusion, our findings would indicate that poor glycemic control impairs the responses of osteoblasts and osteoclasts to 1,25(OH)2D3 in normo-**insulinemic** type 2 **diabetic** patients.
ST calcitriol NIDDM osteoblast glycemia
IT **Diabetes mellitus**
(non-**insulin**-dependent; poor glycemic control impairs response of biochem. parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in humans with NIDDM)
IT Osteoblast

(poor glycemic control impairs response of biochem. parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in humans with NIDDM)

IT Osteocalcins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(poor glycemic control impairs response of biochem. parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in humans with NIDDM)

IT **50-99-7**, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**blood**; poor glycemic control impairs response of biochem. parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in humans with NIDDM)

IT **32222-06-3**, Calcitriol
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(poor glycemic control impairs response of biochem. parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in humans with NIDDM)

IT 9002-64-6, Parathyroid hormone
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(poor glycemic control impairs response of biochem. parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in humans with NIDDM)

RE.CNT 36

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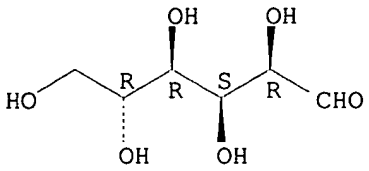
IT **50-99-7**, D-Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); **THU**

(Therapeutic use)
(**blood**; poor glycemic control impairs response of biochem. parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in humans with NIDDM)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L81 ANSWER 8 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:233899 HCAPLUS
DN 130:296893
TI Preparation of novel vitamin D derivatives with cyclopropyl ring in the lateral chains and their pharmaceutical uses
IN Steinmeyer, Andreas; Neef, Gunter; Kirsch, Gerald; Schwarz, Katica; Wiesinger, Herbert; Haberey, Martin; Fahnrich, Marianne; Langer, Gernot
PA Schering A.-G., Germany
SO PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM C07C401-00
ICS A61K031-59
CC 32-7 (Steroids)
Section cross-reference(s): 1, 2, 63
FAN.CNT 1

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	WO 1998-EP6159	W	19980929		

OS MARPAT 130:296893
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; Y1 = H, OH, F, Cl, Br, hydrocarbylcarbonyloxy; Y2 = H, hydrocarbylcarbonyl; R1, R2 = H, or R1R2 = CH2; R3, R4 = H, Cl, F, alkyl, or R3R4 = CH2, or R3R4C = carbocyclic ring; VW = bond, or V = OH and W = H; Q = hydrocarbyl optionally possessing OH which may be etherified or esterified, CO, NH2, halo; Z = hydrocarbyl optionally

possessing CO, OH which may be etherified or esterified, NH2, F, Cl, Br], useful for treating disorders such as calcium absorption disorders, hyperproliferative skin disorders, pruritus, tumors, immunol. disorders, inflammation, rheumatoid arthritis, asthma, autoimmune diseases, multiple sclerosis, **diabetes mellitus**, AIDS, as well as rejection in organ transplantation, are prepd. Thus, sulfone II (also prepd.) was reacted with III (also prepd.) in THF contg. diisopropylamine and BuLi to give, after elimination reaction and deprotection, the title compd. IV. This had an affinity to the calcitriol receptor comparable to that of calcitriol.

ST vitamin D deriv cyclopropane ring prepn; calcium vitamin D deriv cyclopropane ring

IT Skin diseases
(hyperproliferative; prepn. of novel vitamin D derivs. with cyclopropyl ring in lateral chains and pharmaceutical uses)

IT Anti-AIDS drugs
Anti-inflammatory drugs
Antiasthmatics
Antidiabetic agents
Antitumor agents
Autoimmune diseases
Immunomodulators
Multiple sclerosis
Pruritus
Rheumatoid arthritis
(prepn. of novel vitamin D derivs. with cyclopropyl ring in lateral chains and pharmaceutical uses)

IT Transplant (organ)
(rejection, drugs for; prepn. of novel vitamin D derivs. with cyclopropyl ring in lateral chains and pharmaceutical uses)

IT **223107-10-6P 223107-11-7P 223107-15-1P**
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223112-57-0P 223112-60-5P 223112-63-8P
223112-64-9P 223112-66-1P 223112-68-3P

223112-69-4P 223112-70-7P 223112-71-8P
223112-72-9P 223112-73-0P 223112-74-1P
223112-75-2P 223112-76-3P 223112-77-4P
223112-78-5P 223112-79-6P 223112-80-9P
223112-81-0P 223112-83-2P 223112-84-3P
223112-85-4P 223112-86-5P 223112-88-7P
223112-89-8P 223112-92-3P 223112-94-5P
223112-96-7P 223112-98-9P 223113-00-6P
223113-02-8P 223113-04-0P 223113-06-2P
223113-08-4P 223113-10-8P 223113-12-0P
223113-14-2P 223113-17-5P 223113-19-7P
223113-21-1P 223113-23-3P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel vitamin D derivs. with cyclopropyl ring in lateral chains and pharmaceutical uses)

IT 75-03-6, Iodoethane 104-15-4, reactions 105-45-3, Methyl acetoacetate 106-93-4, 1,2-Dibromoethane 107-08-4, 1-Iodopropane 107-21-1, 1,2-Ethanediol, reactions 108-98-5, Thiophenol, reactions 542-69-8, 1-Iodobutane 628-17-1, 1-Iodopentane 638-45-9, 1-Iodohexane 4202-14-6 4762-26-9, Hexyltriphenylphosphonium bromide 5927-18-4, Methyl dimethylphosphonoacetate 6228-47-3, Propyltriphenylphosphonium bromide 13423-48-8, Heptyltriphenylphosphonium bromide 21406-61-1, Pentyltriphenylphosphonium bromide 112828-13-4 223109-38-4
RL: RCT (Reactant)
(prepn. of novel vitamin D derivs. with cyclopropyl ring in lateral chains and pharmaceutical uses)

IT 16278-06-1P 16278-12-9P 22348-95-4P 22348-96-5P 30414-54-1P
38806-09-6P 39815-78-6P 51756-07-1P 62441-58-1P 109765-86-8P
112924-91-1P 124572-91-4P 124572-92-5P 124573-09-7P 223106-04-5P
223106-10-3P 223106-17-0P 223106-22-7P 223106-24-9P 223106-31-8P
223106-40-9P 223106-46-5P 223106-51-2P 223106-56-7P 223106-61-4P
223106-64-7P 223106-67-0P 223106-68-1P 223106-70-5P 223106-72-7P
223106-73-8P 223106-74-9P 223106-75-0P 223106-76-1P 223106-77-2P
223106-78-3P 223106-79-4P 223106-80-7P 223106-81-8P 223106-82-9P
223106-83-0P 223106-84-1P 223106-85-2P 223106-86-3P 223106-87-4P
223106-88-5P 223106-89-6P 223106-90-9P 223106-91-0P 223106-92-1P
223106-93-2P 223106-94-3P 223106-95-4P 223106-96-5P 223106-97-6P
223106-98-7P 223106-99-8P 223107-00-4P 223107-01-5P 223107-02-6P
223107-03-7P 223107-04-8P 223107-05-9P 223107-06-0P 223107-07-1P
223107-08-2P 223107-09-3P 223107-12-8P 223107-13-9P 223107-14-0P
223107-17-3P 223107-18-4P 223107-19-5P 223107-22-0P 223107-23-1P
223107-24-2P **223107-26-4P** 223107-27-5P 223107-28-6P
223107-29-7P 223107-32-2P 223107-33-3P 223107-34-4P 223107-37-7P
223107-38-8P 223107-39-9P 223107-40-2P 223107-41-3P 223107-42-4P
223107-43-5P 223107-44-6P 223107-45-7P 223107-46-8P 223107-47-9P
223107-48-0P 223107-49-1P 223107-50-4P 223107-51-5P 223107-52-6P
223107-53-7P 223107-54-8P 223107-55-9P 223107-56-0P 223107-57-1P
223107-58-2P 223107-59-3P 223107-60-6P 223107-61-7P 223107-62-8P
223107-63-9P 223107-64-0P 223107-65-1P 223107-66-2P 223107-67-3P
223107-68-4P 223107-69-5P 223107-77-5P 223107-78-6P 223107-79-7P
223107-82-2P 223107-83-3P 223107-84-4P 223107-87-7P 223107-88-8P
223107-89-9P 223107-92-4P 223107-93-5P 223107-94-6P 223107-97-9P
223107-98-0P 223107-99-1P 223108-00-7P 223108-01-8P 223108-02-9P
223108-03-0P 223108-04-1P 223108-05-2P 223108-06-3P 223108-07-4P
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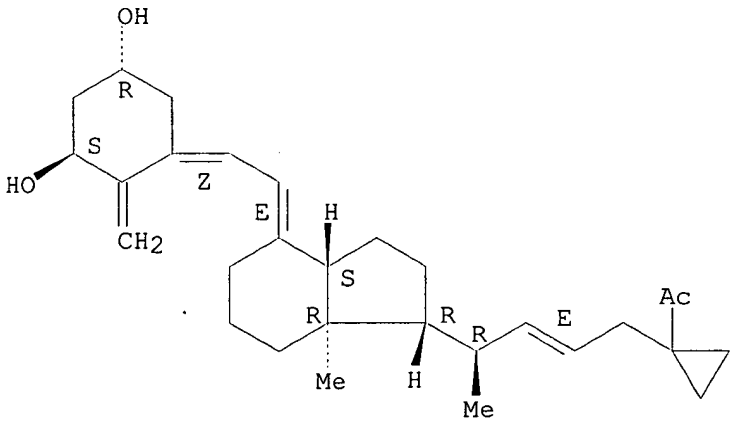
223108-15-4P 223108-16-5P 223108-18-7P 223108-19-8P 223108-22-3P
223108-23-4P 223108-24-5P 223108-25-6P 223108-26-7P 223108-28-9P
223108-29-0P 223108-30-3P 223108-31-4P 223108-32-5P 223108-34-7P
223108-35-8P 223108-36-9P 223108-37-0P 223108-38-1P 223108-40-5P
223108-42-7P 223108-43-8P 223108-44-9P 223108-45-0P 223108-46-1P
223108-47-2P 223108-48-3P 223108-49-4P 223108-50-7P 223108-51-8P
223108-52-9P 223108-53-0P 223108-54-1P 223108-55-2P 223108-58-5P
223108-59-6P 223108-60-9P 223108-61-0P 223108-64-3P 223108-65-4P
223108-66-5P 223108-67-6P 223108-70-1P 223108-71-2P 223108-72-3P

223108-74-5P 223108-76-7P 223108-77-8P 223108-78-9P 223108-79-0P
223108-82-5P 223108-83-6P 223108-85-8P 223108-87-0P 223108-91-6P
223108-94-9P 223108-97-2P 223108-99-4P 223109-01-1P 223109-02-2P
223109-06-6P 223109-07-7P 223109-10-2P 223109-11-3P 223109-13-5P
223109-14-6P 223109-16-8P 223109-18-0P 223109-23-7P 223109-25-9P
223109-26-0P 223109-32-8P 223109-49-7P **223109-54-4P**
223109-65-7P 223109-74-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of novel vitamin D derivs. with cyclopropyl ring in lateral chains and pharmaceutical uses)
IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. of novel vitamin D derivs. with cyclopropyl ring in lateral chains for calcium absorption regulation)
RE.CNT 3
RE
(1) Leo Pharmaceutical Poducts Ltd; WO 8910351 A 1989 HCAPLUS
(2) Leo Pharmaceutical Products Ltd; WO 8700834 A 1987 HCAPLUS
(3) Schering Ag; WO 9700242 A 1997 HCAPLUS
IT **223107-10-6P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel vitamin D derivs. with cyclopropyl ring in lateral chains and pharmaceutical uses)
RN 223107-10-6 HCAPLUS
CN Ethanone, 1-[1-[(1.alpha.,3.beta.,5Z,7E,22E)-1,3-dihydroxy-9,10-secochola-5,7,10(19),22-tetraen-24-yl]cyclopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 9 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:77538 HCAPLUS
DN 130:139510
TI Preparation of dihomo-seco-cholestanes with two unsaturated bonds in the side chain
IN Barbier, Pierre; Mohr, Peter; Muller, Marc; Self, Christopher
PA F.Hoffmann-La Roche A.-G., Switz.
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59
CC 32-7 (Steroids)
Section cross-reference(s): 1, 2, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9903828	A1	19990128	WO 1998-EP4293	19980710
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9888602	A1	19990210	AU 1998-88602	19980710
	EP 998455	A1	20000510	EP 1998-940201	19980710
	R: DE, ES, FR, GB, IT				
	JP 2001510183	T2	20010731	JP 2000-503057	19980710
	US 5994569	A	19991130	US 1998-115188	19980714
PRAI	EP 1997-112225	A	19970717		
	WO 1998-EP4293	W	19980710		

OS MARPAT 130:139510

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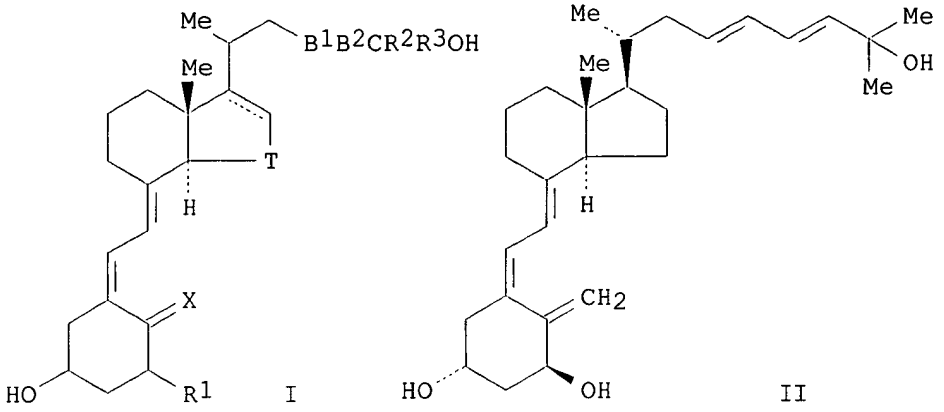


AB Polyunsatd. 24a,24b-dihomo-9,10-secocholestane derivs. of formula I [B1, B2 = CH=CH, C.tplbond.C; T = CH2, CH2CH2; X = H2, CH2; R1 = H, F, OH; R2, R3 = alkyl, CF3; CR2R3 = cycloalkyl] are prepd. and are useful in the treatment or prevention of vitamin D dependent disorders and of IL-12-dependent autoimmune diseases, particularly psoriasis, basal cell carcinomas, disorders of keratinization and keratosis, leukemia, osteoporosis, hyperparathyroidism accompanying renal failure, multiple sclerosis, transplant rejection, graft vs. host disease, rheumatoid arthritis, **insulin**-dependent **diabetes mellitus** , inflammatory bowel disease, septic shock and allergic encephalomyelitis. Thus, II was prepd. and was found to have an IC50 for the inhibition of IL-12 prodn. of 10 nM. Pharmaceutical compns. contg. I are described.

ST cholestane dihomoseco prepn vitamin D dependent disorder; dihomosecocholestane prepn vitamin D dependent disorder

IT Allergic encephalomyelitis
Autoimmune diseases
Basal cell carcinoma
Graft vs. host reaction
Hyperparathyroidism
Inflammatory bowel diseases
Insulin dependent diabetes mellitus
Keratosis
Leukemia
Multiple sclerosis

Osteoporosis
Psoriasis
Renal failure
Rheumatoid arthritis
Septic shock
Transplant rejection
(prepn. of polyunsatd. dihomosecocholestanes for the treatment of vitamin D dependent disorders)

IT 9,10-Secosteroids
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polyunsatd. dihomosecocholestanes for the treatment of vitamin D dependent disorders)

IT **219976-31-5P 219976-32-6P 219976-33-7P**
219976-34-8P 219976-35-9P 219976-36-0P 219976-37-1P 219976-38-2P
219976-39-3P 219976-40-6P **219976-41-7P 219976-42-8P**
219976-43-9P 219976-44-0P 219976-45-1P
219976-46-2P 219976-47-3P 219976-48-4P
219976-49-5P 219976-50-8P 219976-51-9P
219976-52-0P 219976-53-1P 219976-54-2P
219976-95-1P 219976-98-4P 219977-01-2P 219977-04-5P 219977-07-8P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polyunsatd. dihomosecocholestanes for the treatment of vitamin D dependent disorders)

IT 67-64-1, Acetone, reactions 96-22-0, 3-Pentanone 120-92-3, Cyclopentanone 684-16-2, Hexafluoroacetone 6089-04-9 13361-64-3, Propargyltrimethylsilane 51594-55-9, (R)-Epichlorohydrin, reactions 76566-95-5, Trimethyl phosphonocrotonate 81522-68-1 100858-27-3 100928-03-8 135217-63-9 139356-39-1 189556-75-0 189556-76-1
RL: RCT (Reactant)
(prepn. of polyunsatd. dihomosecocholestanes for the treatment of vitamin D dependent disorders)

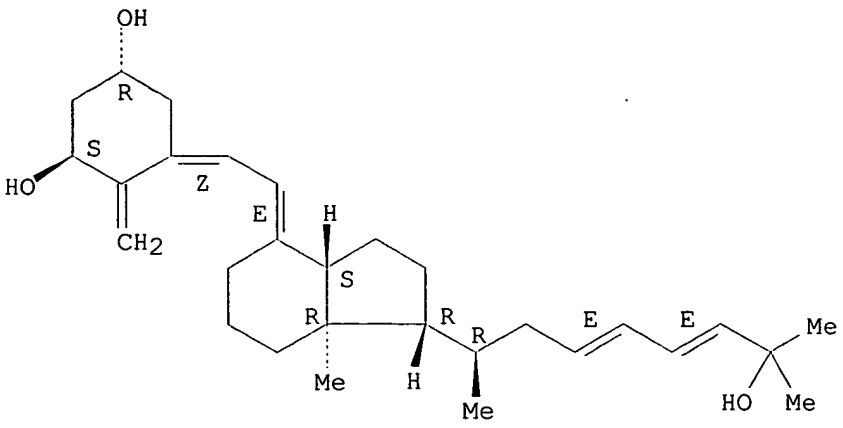
IT 93489-71-5P 214777-16-9P 219976-55-3P 219976-56-4P 219976-57-5P
219976-58-6P 219976-59-7P 219976-60-0P 219976-61-1P 219976-62-2P
219976-63-3P 219976-64-4P 219976-65-5P 219976-66-6P 219976-67-7P
219976-68-8P 219976-69-9P 219976-70-2P 219976-71-3P 219976-72-4P
219976-73-5P 219976-74-6P 219976-75-7P 219976-76-8P 219976-77-9P
219976-78-0P 219976-79-1P 219976-80-4P 219976-81-5P 219976-82-6P
219976-83-7P 219976-84-8P 219976-85-9P 219976-86-0P 219976-87-1P
219976-88-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of polyunsatd. dihomosecocholestanes for the treatment of vitamin D dependent disorders)

RE.CNT 6
RE
(1) Allewaert, K; STEROIDS: STRUCTURE, FUNCTION, AND REGULATION 1995, V60(4), P324 HCAPLUS
(2) Chodynski, M; STEROIDS: STRUCTURE, FUNCTION, AND REGULATION 1997, V62(7), P546 HCAPLUS
(3) Duphar Int Res; EP 0742203 A 1996 HCAPLUS
(4) Galverley, M; WO 9818759 A 1998 HCAPLUS
(5) Schering Ag; EP 0441467 A 1991 HCAPLUS
(6) Wijnsma, A; Steroids 1998, V62(7), P546

IT **219976-31-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polyunsatd. dihomosecocholestanes for the treatment of vitamin D dependent disorders)

RN 219976-31-5 HCAPLUS
CN 1,3-Cyclohexanediol, 4-methylene-5-[(2E)-[(1R,3aS,7aR)-octahydro-1-[(1R,3E,5E)-7-hydroxy-1,7-dimethyl-3,5-octadienyl]-7a-methyl-4H-inden-4-ylidene]ethylidene]-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 10 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:27811 HCAPLUS
DN 130:81699
TI Preparation of vitamin D3 derivatives as remedies for inflammatory respiratory diseases and other disorders
IN Tanaka, Hiroko; Gao, Qingzhi; Manabe, Kenji; Furuya, Minoru; Tabe, Masayasu; Ishizuka, Seiichi; Chokki, Manabu; Mitsuhashi, Hiroaki; Kishimoto, Tadashi; Hazato, Atsuo; Sakuma, Yasuji
PA Teijin Limited, Japan
SO PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07C401-00
ICS A61K031-59
CC 32-7 (Steroids)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9858909	A1	19981230	WO 1998-JP2813	19980624
	W: AU, CA, CN, JP, KR, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9879328	A1	19990104	AU 1998-79328	19980624
	EP 970948	A1	20000112	EP 1998-929661	19980624
	R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, SE				
	US 6028208	A	20000222	US 1999-242665	19990222
PRAI	JP 1997-168803		19970625		
	WO 1998-JP2813		19980624		

OS MARPAT 130:81699
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Vitamin D3 derivs. [I; R1, R2 = H, trialkylsilyl, etc.; Z = Q, Q1, Q2; R3, R4 = H, OH, etc.; R5-R8 = H, OH, alkyl, acyloxy; R9 = H, OH, alkyl, alkylthio; R10 = H, alkyl, alkoxy; A, B = H, OH, etc.; X, Y = carbonyl oxygen, or one of X and Y = H while another = OH, etc.; X1 = (CH2)n; X2 = (CH2)m; n, m = 0-2; X3 = (CR7R8)m], useful for treatment of inflammatory respiratory diseases, malignant tumors, articular rheumatism,

osteoporosis, **diabetes mellitus**, hypertension, baldness, acne, psoriasis, and dermatitis, are prepd. Thus, II [R11 = CHO] was reacted with 2-ethyl-2-hydroxy-2-cyclopentanone in ethanol contg. KOH to give a mixt. of all 4 possible stereoisomers of the final product [II; R11 = Q3]. One of these stereoisomers showed >40% inhibitor of neutrocyte infiltration in induced pneumonia in hamsters. Pharmaceutical compns. contg. I are described.

ST vitamin D3 deriv prepn; inflammatory respiratory disorder therapy vitamin D3

IT Antirheumatic drugs
(for articular rheumatism; prepn. of vitamin D3 derivs. as remedies for inflammatory respiratory diseases and other disorders)

IT Anti-inflammatory drugs
(for respiratory diseases; prepn. of vitamin D3 derivs. as remedies for inflammatory respiratory diseases and other disorders)

IT Antiarthritics
(prepn. of vitamin D3 derivs. as remedies for articular rheumatism and other disorders)

IT Acne
Alopecia
Antidiabetic agents
Antihypertensives
Antiosteoporotic agents
Antitumor agents
Dermatitis
Neutrophil
Psoriasis
Respiratory tract diseases
(prepn. of vitamin D3 derivs. as remedies for inflammatory respiratory diseases and other disorders)

IT **218437-01-5P 218437-02-6P 218437-03-7P**
218437-04-8P 218437-05-9P 218437-06-0P
218437-07-1P 218437-08-2P 218437-09-3P
218437-10-6P 218437-11-7P 218437-13-9P
218437-15-1P 218437-17-3P 218437-19-5P
218437-21-9P 218437-23-1P 218437-24-2P
218437-25-3P 218437-26-4P 218437-27-5P
218437-28-6P 218437-29-7P 218437-30-0P
218437-31-1P 218437-32-2P 218437-33-3P
218437-34-4P 218437-35-5P 218437-36-6P
218437-37-7P 218437-38-8P 218437-39-9P
218437-40-2P 218437-41-3P 218437-42-4P
218437-43-5P 218437-44-6P 218437-45-7P
218437-46-8P 218437-47-9P 218437-48-0P
218437-49-1P 218437-50-4P 218437-51-5P
218437-52-6P 218437-53-7P 218437-54-8P
218437-55-9P 218437-56-0P 218437-57-1P
218437-58-2P 218437-59-3P 218437-60-6P
218437-61-7P 218437-62-8P 218437-63-9P
218437-64-0P 218437-65-1P 218437-66-2P
218437-67-3P 218598-74-4P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of vitamin D3 derivs. as remedies for inflammatory respiratory diseases and other disorders)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. of vitamin D3 derivs. as remedies for inflammatory respiratory diseases and other disorders)

IT 75-77-4, Trimethylsilyl chloride, reactions 108-94-1, Cyclohexanone, reactions 1034-49-7 1120-72-5, 2-Methyl-1-cyclopentanone 2605-67-6 4541-32-6, 2,2-Dimethyl-1-cyclopentanone 55767-60-7 64190-52-9 112924-91-1 160156-85-4 161055-41-0 173388-41-5 218437-98-0 218437-99-1 218438-01-8 218438-02-9
RL: RCT (Reactant)

(prepn. of vitamin D3 derivs. as remedies for inflammatory respiratory diseases and other disorders)

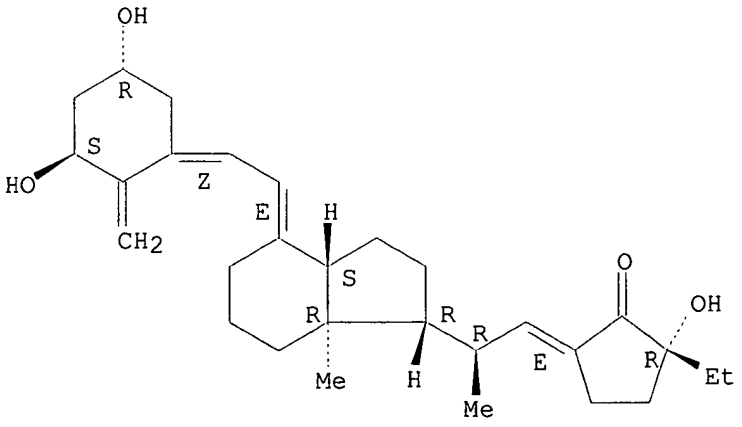
IT 96845-30-6P 171283-36-6P 175271-49-5P 218437-68-4P 218437-69-5P
218437-70-8P 218437-71-9P 218437-72-0P 218437-73-1P 218437-74-2P
218437-75-3P 218437-76-4P 218437-77-5P 218437-78-6P 218437-79-7P
218437-80-0P 218437-81-1P 218437-83-3P 218437-84-4P 218437-85-5P
218437-86-6P 218437-87-7P 218437-89-9P 218437-90-2P 218437-91-3P
218437-92-4P 218437-93-5P 218437-95-7P 218437-96-8P 218598-76-6P
218598-79-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of vitamin D3 derivs. as remedies for inflammatory respiratory diseases and other disorders)

RE.CNT 8
RE
(1) Leo Pharmaceutical Products Ltd; EP 412110 A1 HCAPLUS
(2) Leo Pharmaceutical Products Ltd; US 5206229 A HCAPLUS
(3) Leo Pharmaceutical Products Ltd; WO 8910351 A1 HCAPLUS
(4) Leo Pharmaceutical Products Ltd; JP 03504377 A 1991
(5) Teijin Ltd; US 5719297 A HCAPLUS
(6) Teijin Ltd; EP 712843 A1 HCAPLUS
(7) Teijin Ltd; WO 9533716 A1 HCAPLUS
(8) Teijin Ltd; JP 853411 A 1996

IT **218437-01-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of vitamin D3 derivs. as remedies for inflammatory respiratory diseases and other disorders)

RN 218437-01-5 HCAPLUS
CN Cyclopentanone, 5-[(2R)-2-[(1R,3aS,4E,7aR)-4-[(2Z)-[(3S,5R)-3,5-dihydroxy-2-methylenecyclohexylidene]ethylidene]octahydro-7a-methyl-1H-inden-1-yl]propylidene]-2-ethyl-2-hydroxy-, (2R,5E)- (9CI) (CA INDEX NAME)

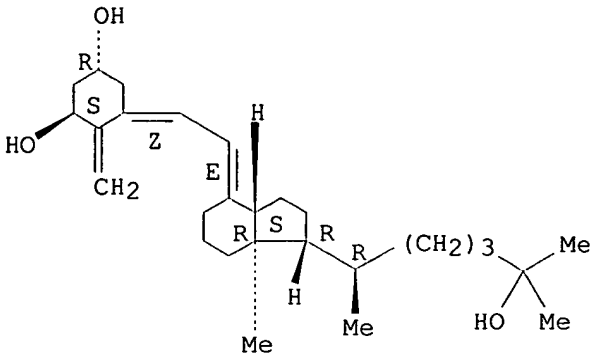
Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 11 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:426975 HCAPLUS
DN 129:184592
TI 1,25-Dihydroxyvitamin D3 restores sensitivity to cyclophosphamide-induced apoptosis in non-obese diabetic (NOD) mice and protects against diabetes
AU Casteels, K.; Waer, M.; Bouillon, R.; Depovere, J.; Valckx, D.; Laureys, J.; Mathieu, C.
CS Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Katholieke Universiteit Leuven, Louvain, 3000, Belg.
SO Clin. Exp. Immunol. (1998), 112(2), 181-187
CODEN: CEXIAL; ISSN: 0009-9104
PB Blackwell Science Ltd.

DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The activated form of vitamin D, 1,25(OH)2D3, and its analogs can prevent **type I diabetes** in NOD mice. Protection is achieved without signs of systemic immunosuppression and is assocd. with a restoration of the defective immune regulator system of the NOD mice. The aim of the present study was to investigate whether this restoration of regulator cell function is the only mechanism in the prevention of **diabetes** by 1,25(OH)2D3. We tested therefore if 1,25(OH)2D3 could prevent cyclophosphamide-induced **diabetes**, since **diabetes** occurring after cyclophosphamide injection is believed to be due to an elimination of suppressor cells. NOD mice treated with 1,25(OH)2D3 (5 .mu.g/kg every 2 days) from the time of weaning were clearly protected against **diabetes** induced by cyclophosphamide (200 mg/kg body wt. at 70 days old) (2/12 (17%) vs. 36/53 (68%) in control mice, P<0.005). By co-transfer expts. it was demonstrated that cyclophosphamide had indeed eliminated the suppressor cells present in 1,25(OH)2D3-treated mice. Since cyclophosphamide injection did not break the protection offered by 1,25(OH)2D3, it was clear that **diabetogenic** effector cells were affected by 1,25(OH)2D3 treatment as well. This was confirmed by the finding that splenocytes from 1,25(OH)2D3-treated mice were less capable of transferring **diabetes** in young, irradiated NOD mice, and by the demonstration of lower Th1 cytokine levels in the pancreas of 1,25(OH)2D3-treated, cyclophosphamide-injected mice. This better elimination of effector cells in 1,25(OH)2D3-treated mice could be explained by a restoration of the sensitivity to cyclophosphamide-induced apoptosis in both thymocytes and splenocytes, in normally apoptosis-resistant NOD mice. Altogether, these data indicate that the protection against **diabetes** offered by 1,25(OH)2D3 may be independent of the presence of suppressor cells, and may involve increased apoptosis of Th1 autoimmune effector cells.
ST dihydroxyvitamin D3 prevention diabetes immune cells
IT Lymphocyte
Splenocyte
Suppressor T cell
Thymocyte
Th1 cell
(1,25-dihydroxyvitamin D3 protection against diabetes in relation to its effect on suppressor and effector immune cells)
IT **Antidiabetic** agents
Apoptosis
Insulin dependent diabetes mellitus
(1,25-dihydroxyvitamin D3 restores sensitivity to cyclophosphamide-induced apoptosis in non-obese **diabetic** mice and protects against **diabetes**)
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(1,25-dihydroxyvitamin D3 restores sensitivity to cyclophosphamide-induced apoptosis in non-obese diabetic mice and protects against diabetes)
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(1,25-dihydroxyvitamin D3 restores sensitivity to cyclophosphamide-induced apoptosis in non-obese diabetic mice and protects against diabetes)
RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 12 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:370506 HCAPLUS
DN 129:130997
TI Prevention of autoimmune destruction of syngeneic islet grafts in spontaneously diabetic nonobese diabetic mice by a combination of a vitamin D3 analog and cyclosporine
AU Casteels, Kristina; Waer, Mark; Laureys, Jos; Valckx, Dirk; Depovere, Jos; Bouillon, Roger; Mathieu, Chantal
CS Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Louvain, 3000, Belg.
SO Transplantation (1998), 65(9), 1225-1232
CODEN: TRPLAU; ISSN: 0041-1337
PB Williams & Wilkins
DT Journal
LA English
CC 1-7 (Pharmacology)
AB **Type 1 diabetes** is characterized by the presence of an autoimmune memory, responsible for the destruction of even syngeneic islet grafts. This recurrence of autoimmunity is partly responsible for the need of extensive immunosuppression in pancreas and islet transplantation in **type 1 diabetic** patients. The aim of the study was to evaluate the capacity of a 20-epi-analog of vitamin D3, KH1060, both alone and in combination with cyclosporine (CsA) to prevent **diabetes** recurrence in syngeneic islet grafts in nonobese **diabetic** (NOD) mice. Spontaneously **diabetic** NOD mice grafted with syngeneic islets under the kidney capsule were treated with KH1060, CsA, or a combination of both drugs from the day before transplantation until recurrence or 60 days after transplantation. Vehicle-treated mice showed a recurrence of **diabetes** in 100% of cases within 4 wk. Treatment with high doses of CsA (15 mg/kg/day) or KH1060 (1 .mu.g/kg/2 days) significantly prolonged islet survival (60 days and 50 days, resp., vs. 9.5 days in controls). Mice treated with subtherapeutical doses of both drugs combined (KH1060 0.5 .mu.g/kg/2 days + CsA 7.5 mg/kg/day) had significant prolongation of graft survival (48 days) and more importantly, four of five mice that were still normoglycemic 60 days after transplantation showed no recurrence after discontinuation of all treatment. Histol. of the grafts of control and combination-treated mice demonstrated that graft infiltration and islet destruction were less severe in grafts of combination-treated mice. Cytokine mRNA anal. in the grafts 6 days after transplantation revealed a clear suppression of interleukin-12 and T helper 1 cytokines and higher levels of interleukin-4 in combination-treated mice. KH1060, an analog of 1,25(OH)2D3, delays autoimmune disease recurrence after syngeneic islet transplantation in NOD mice, both alone and esp. in combination with CsA, possibly restoring tolerance to .beta. cells in 30% of cases.
ST syngeneic islet graft cyclosporine vitamin D3; immunosuppressant syngeneic islet graft autoimmune destruction
IT mRNA

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cytokine-encoding; prevention of autoimmune destruction of syngeneic islet grafts in diabetic nonobese diabetic mice by combination of vitamin D3 analog and cyclosporine in relation to cytokine prodn. and calcium metab. and bone remodeling)

IT Interferon .gamma.
Interleukin 10
Interleukin 12
Interleukin 2
Interleukin 4
Transforming growth factors .beta.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mRNA encoding; prevention of autoimmune destruction of syngeneic islet grafts in diabetic nonobese diabetic mice by combination of vitamin D3 analog and cyclosporine in relation to cytokine prodn. and calcium metab. and bone remodeling)

IT Autoimmune diseases
Bone formation
Drug interactions
Immunosuppressants
Insulin dependent diabetes mellitus
Islet transplant
(prevention of autoimmune destruction of syngeneic islet grafts in **diabetic** nonobese **diabetic** mice by combination of vitamin D3 analog and cyclosporine in relation to cytokine prodn. and calcium metab. and bone remodeling)

IT Osteocalcins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prevention of autoimmune destruction of syngeneic islet grafts in diabetic nonobese diabetic mice by combination of vitamin D3 analog and cyclosporine in relation to cytokine prodn. and calcium metab. and bone remodeling)

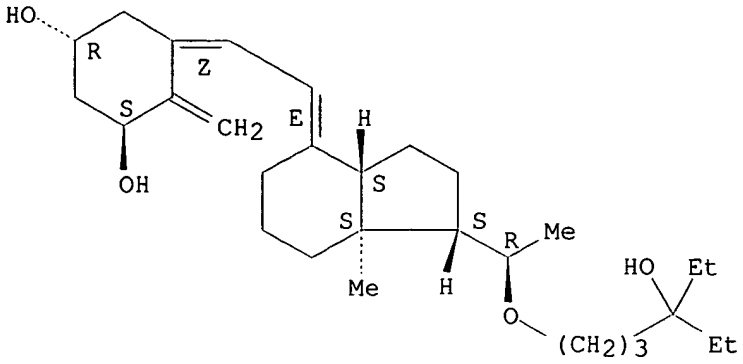
IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab.; prevention of autoimmune destruction of syngeneic islet grafts in diabetic nonobese diabetic mice by combination of vitamin D3 analog and cyclosporine in relation to cytokine prodn. and calcium metab. and bone remodeling)

IT 59865-13-3, Cyclosporine **131875-08-6**, KH1060
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prevention of autoimmune destruction of syngeneic islet grafts in diabetic nonobese diabetic mice by combination of vitamin D3 analog and cyclosporine in relation to cytokine prodn. and calcium metab. and bone remodeling)

IT **131875-08-6**, KH1060
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prevention of autoimmune destruction of syngeneic islet grafts in diabetic nonobese diabetic mice by combination of vitamin D3 analog and cyclosporine in relation to cytokine prodn. and calcium metab. and bone remodeling)

RN 131875-08-6 HCAPLUS
CN 1,3-Cyclohexanediol, 5-[(2E)-[(1S,3aS,7aS)-1-[(1R)-1-[(4-ethyl-4-hydroxyhexyl)oxy]ethyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

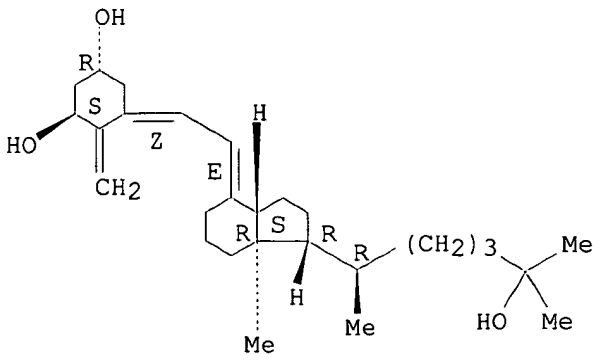
Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 13 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:309212 HCAPLUS
DN 129:76953
TI 1,25-Dihydroxyvitamin D3 corrects insulin and lipid abnormalities in **uremia**
AU Mak, Robert H. K.
CS Division of Nephrology, Department of Pediatrics, Oregon Health Sciences University, Portland, OR, USA
SO Kidney Int. (1998), 53(5), 1353-1357
CODEN: KDYIA5; ISSN: 0085-2538
PB Blackwell Science, Inc.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The effect of i.v. 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] therapy on insulin and lipid metab. was examd. in patients on maintenance hemodialysis (HD). Eight patients (Group I, 19 yr old) were studied before and after four weeks of i.v. 1,25(OH)2D3 therapy (1.8 .mu.g), during which time the serum parathyroid hormone (PTH) concns. did not change. Another eight patients (Group II, 18 yr old) were studied before and after four weeks of oral dihydrotachysterol (0.8 mg). Serum PTH also did not change in Group II. Serum glucose concns. during an oral glucose tolerance test (OGTT) were higher in Group I before 1,25(OH)2D3 compared with controls and these normalized following four weeks of i.v. 1,25(OH)2D3. Serum glucose concns. during OGTT were also higher in Group II before DHT compared with controls and did not change following four weeks of oral DHT. Insulin sensitivity during euglycemic clamp studies in Group I before 1,25(OH)2D3 (223 mg/m2/min) was low compared with controls (320 mg/m2/min) and was normalized following therapy (315 mg/m2/min). Insulin sensitivity was also low in Group II at the beginning of the study and did not change at the end of the four week period. Both early-phase and late-phase insulin secretion were low in Group I before 1,25(OH)2D3 compared with controls and normalized following i.v. 1,25(OH)2D3 therapy. Both early-phase and late-phase insulin secretion were also low in Group II at the beginning of the study and did not change at the end of the four week period of DHT treatment. Plasma triglycerides were elevated in Group I patients before treatment (198 mg/dL) compared with controls (139 mg/dL) and were normalized (148 mg/dL) following i.v. 1,25(OH)2D3 therapy. Plasma total cholesterol and high d. lipoprotein cholesterol were normal before treatment compared with controls and did not change following i.v. 1,25(OH)2D3 therapy. Plasma triglycerides, total cholesterol and high d. lipoprotein cholesterol did not change in Group II during the study period. Thus, i.v. 1,25(OH)2D3 therapy cor. glucose intolerance, insulin resistance, hypoinsulinemia as well as hypertriglyceridemia in patients on HD, in the absence of PTH suppression.
ST dihydroxyvitamin D insulin lipid abnormality uremia
IT Hemodialysis
Hypertriglyceridemia
Hypoinsulinemia

Insulin resistance
Lipid metabolism
Plasma (blood)
Renal failure
Serum (blood)
(dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia in humans)
IT Blood cholesterol
Blood glucose
Blood lipids
Blood triglycerides
High-density lipoproteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia in humans)
IT 67-96-9, Dihydrotachysterol 9002-64-6, Parathyroid hormone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia in humans)
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia in humans)
IT **9004-10-8**, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia in humans)
IT **50-99-7**, Glucose, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(tolerance; dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia in humans)
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia in humans)
RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 14 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:11860 HCAPLUS
DN 128:124074
TI Prevention of **type I diabetes** in nonobese

diabetic mice by late intervention with nonhypercalcemic analogs of 1,25-dihydroxyvitamin D3 in combination with a short induction course of cyclosporin A

AU Casteels, Kristina M.; Mathieu, Chantal; Waer, Mark; Valckx, Dirk; Overbergh, Lut; Laureys, Jos M.; Bouillon, Roger

CS Lab. for Experimental Medicine and Endocrinology and Lab. for Experimental Transplantation, Gatsthuisberg, 3000, Belg.

SO Endocrinology (1998), 139(1), 95-102
CODEN: ENDOAO; ISSN: 0013-7227

PB Endocrine Society

DT Journal

LA English

CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 1, 15

AB In nonobese **diabetic** (NOD) mice, **type I** **diabetes** can be prevented without generalized immunosuppression by nonhypercalcemic analogs of vitamin D3 when treatment is started early, i.e., before the autoimmune attack, reflected by insulitis, occurs. The aim of this study was to investigate whether these substances can arrest progression to clin. overt **diabetes** when administered in a more advanced disease stage, namely when the autoimmune attack is ongoing, reflecting the situation in **prediabetic** subjects in whom immune intervention is being considered. The authors, therefore, evaluated the protective potential of MC1288 (20-epi-1,25-dihydroxyvitamin D3) a nonhypercalcemic analog of 1,25-dihydroxyvitamin D3, both alone and in combination with a short induction course of cyclosporin A, in NOD mice that already have insulitis, as demonstrated in pancreatic biopsies performed 15 days before the start of therapy. Subsequently, mice were randomized into a control group, receiving the treatment vehicle, and three treatment groups, receiving, resp., 5 mg/kg/day cyclosporin A (CyA) from days 85-105, 0.1 .mu.g/kg/2 days MC1288 from days 85-200, or the combination of these two regimens. At the time of the pancreatic biopsy (day 70), insulitis was evenly distributed in all groups, and 27.7% of the islets scored showed signs of destructive insulitis. **Diabetes** out-come by 200 days was 74% (14 of 19) in the CyA-treated group, comparable to the **diabetes** incidence in control mice (65%; 17 of 26). Treatment with CM1288 alone could not reduce disease incidence (70%; 14 of 20), but the combination therapy reduced **diabetes** incidence to 25% (7 of 20). All treatments were well tolerated, without major side-effects on calcium or bone metab. and without signs of generalized immunosuppression. Cotransfer expts. could not reveal the induction of suppressor cells. Reverse transcription-PCR on pancreatic tissue revealed significantly lower levels of interferon-.gamma. and higher levels of interleukin-4 in the combination group. In conclusion, nonhypercalcemic analogs of 1,25-dihydroxyvitamin D3 administered to NOD mice when the autoimmune disease is already active can prevent clin. **diabetes** when this therapy is combined with a short induction course of an immunosuppressant such as CyA.

ST dihydroxyvitamin D3 cyclosporin A diabetes; antidiabetic calcitriol analog immunosuppressant cyclosporin A

IT **Antidiabetic** agents
Bone resorption
Hypercalcemia
Immunosuppression
Insulin dependent diabetes mellitus
Insulitis
Serum (blood)
Urine
(**type I diabetes** prevention in nonobese **diabetic** mice by late intervention with nonhypercalcemic analogs of dihydroxyvitamin D3 in combination with cyclosorin A)

IT Interferon .gamma.
Interleukin 4
Osteocalcins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**type I diabetes** prevention in nonobese

diabetic mice by late intervention with nonhypercalcemic analogs of dihydroxyvitamin D3 in combination with cyclosorin A)

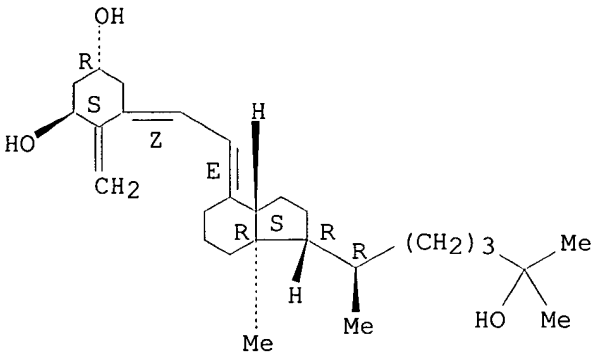
IT **32222-06-3D**, 1,25-Dihydroxyvitamin D3, analogs 59865-13-3, Cyclosporin A **134523-84-5**, MC1288
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**type I diabetes** prevention in nonobese **diabetic** mice by late intervention with nonhypercalcemic analogs of dihydroxyvitamin D3 in combination with cyclosorin A)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**type I diabetes** prevention in nonobese **diabetic** mice by late intervention with nonhypercalcemic analogs of dihydroxyvitamin D3 in combination with cyclosorin A)

IT **32222-06-3D**, 1,25-Dihydroxyvitamin D3, analogs
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**type I diabetes** prevention in nonobese **diabetic** mice by late intervention with nonhypercalcemic analogs of dihydroxyvitamin D3 in combination with cyclosorin A)

RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



c/ Lee 2 10-1-01

L81 ANSWER 15 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:722085 HCAPLUS
DN 128:493
TI Vitamin D and diabetes
AU Mathieu, Chantal; Casteels, Kristina; Bouillon, Roger
CS Lab. Experimental Med. Endocrinol., Catholic Univ. Leuven, Belg.
SO Vitam. D (1997), 1183-1196. Editor(s): Feldman, David; Glorieux, Francis H.; Pike, J. Wesley. Publisher: Academic, San Diego, Calif.
CODEN: 65GCAB
DT Conference; General Review
LA English
CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 14
AB A review, with 91 refs., on the effects of vitamin D and its active form, 1,25-dihydroxyvitamin D3, on the pathogenesis of **diabetes**. Topics covered were: vitamin D and .beta.-cell; vitamin D and the immune system in **diabetes mellitus**; and clin. perspectives.
ST vitamin D diabetes review; antidiabetic dihydroxyvitamin D3 review
IT **Antidiabetic** agents
(vitamin D and diabetes)
IT **1406-16-2**, Vitamin D **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU**

(Therapeutic use); BIOL (Biological study); USES (Uses)
(vitamin D and diabetes)
IT **1406-16-2**, Vitamin D
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(vitamin D and diabetes)
RN 1406-16-2 HCAPLUS
CN Vitamin D (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L81 ANSWER 16 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:609667 HCAPLUS
DN 127:243262
TI Methods and compositions for primary and secondary prevention of autoimmune diabetes using vitamin D analogs and optional second immunomodulator
IN Mathieu, Chantal; Waer, Mark; Bouillon, Roger
PA K.U. Leuven Research & Development, Belg.
SO U.S., 11 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K009-20
NCL 424464000
CC 1-7 (Pharmacology)
Section cross-reference(s): 63

Printed 10-1-01

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5665387	A	19970909	US 1994-299936	19940901

OS MARPAT 127:243262
AB A method is disclosed for modulating the immune system by administering one or more vitamin D (analogs) to a subject in need of immune therapy; the method may, but need not, include simultaneous treatment with a second immune system-modulating active agent. Preferably, the treatment method is used to induce primary or secondary prevention of **type I diabetes** in a subject susceptible to **type I diabetes**. Administration of the vitamin D (analogs) is enteral or parenteral. The vitamin D analog is e.g. 1,25-dihydroxyvitamin D3 or KH1060 (1.alpha.,25-dihydroxy-20-epi-22-oxa-24,26,27-trishomovitamin D). KH1060 prevented insulitis and **diabetes** in the spontaneously **diabetic** NOD mouse. KH1060 also prolonged survival of syngeneic islet grafts in spontaneously **diabetic** NOD mice, both alone and in synergy with cyclosporin A.
ST vitamin D analog immunomodulation diabetes; antidiabetic vitamin D analog; dihydroxy vitamin D3 immunomodulation diabetes; KH1060 immunomodulation diabetes; islet transplant KH1060 cyclosporin A
IT Drug delivery systems
(enteric; vitamin D analogs and optional second immunomodulator for primary and secondary prevention of autoimmune diabetes)
IT Bone
(vitamin D analog effect on calcium metab.)
IT Osteocalcins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(vitamin D analog effect on calcium metab.)
IT **Antidiabetic** agents
Capsules (drug delivery systems)
Drug delivery systems
Emulsions (drug delivery systems)
Immunomodulators
Insulin dependent diabetes mellitus
Islet transplant
Parenteral solutions (drug delivery systems)
Powders (drug delivery systems)
Solutions (drug delivery systems)

Suppressor T cell
Suspensions (drug delivery systems)
Synergistic drug interactions
Tablets (drug delivery systems)
(vitamin D analogs and optional second immunomodulator for primary and secondary prevention of autoimmune **diabetes**)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(vitamin D analog effect on calcium metab.)

IT **1406-16-2D**, Vitamin D, analogs **32222-06-3**, 1,25-Dihydroxyvitamin D3 59865-13-3, Cyclosporin A **131875-08-6**, KH1060
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(vitamin D analogs and optional second immunomodulator for primary and secondary prevention of autoimmune diabetes)

IT **9004-10-8**, **Insulin**, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(vitamin D analogs and optional second immunomodulator for primary and secondary prevention of autoimmune **diabetes**)

IT **1406-16-2D**, Vitamin D, analogs
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(vitamin D analogs and optional second immunomodulator for primary and secondary prevention of autoimmune diabetes)

RN 1406-16-2 HCAPLUS
CN Vitamin D (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L81 ANSWER 17 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:148719 HCAPLUS
DN 126:152822
TI **RXR** receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily
IN Demarchez, Michel; Jomard, Andre
PA Centre International De Recherches Dermatologiques Galderma (C.I.R.D. Galderma), Fr.
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA French
IC ICM A61K031-59
ICS A61K031-20; A61K031-19
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 749752	A1	19961227	EP 1996-401140	19960528
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	FR 2735367	A1	19961220	FR 1995-7300	19950619
	FR 2735367	B1	19970718		
	AU 9654703	A1	19970116	AU 1996-54703	19960604
	AU 688216	B2	19980305		
	CA 2179426	AA	19961220	CA 1996-2179426	19960618
	JP 09002972	A2	19970107	JP 1996-157267	19960618
	US 6004987	A	19991221	US 1996-666799	19960619
PRAI	FR 1995-7300		19950619		

AB RXR-specific ligands are used for the prepn. of systemic compns. to augment the cell proliferation-modulating and cell differentiation-modulating activity of topically applied ligands of the steroid/thyroid receptor superfamily, other than RXR receptor-specific ligands, and able to heterodimerize with RXRs. The compns. of the invention may be used to

treat skin disorders, skin aging, cancers, alopecia, problems with sebaceous gland function, etc. The synergistic effect of an RXR ligand [4-((3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl)benzoic acid] and an RAR ligand [2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-6-benzo[b]thiophenecarboxylic acid] is described. Oral and topical formulations are included.

ST RXR ligand steroid receptor ligand therapeutic; thyroid receptor ligand RXR ligand therapeutic; cosmetic RXR ligand combination; skin disorder RXR ligand combination

IT Alopecia
Anti-inflammatory drugs
Antiatherosclerotics
Antidiabetic agents
Antiobesity agents
Antitumor agents
Antiviral agents
Cardiovascular agents
Cell differentiation
Cell proliferation
Cosmetics
Creams (drug delivery systems)
Eye diseases
Fungicides
Immunological diseases
Lotions (drug delivery systems)
Ointments (drug delivery systems)
Oral drug delivery systems
Skin aging
Skin diseases
Skin pigmentation disorders
Suspensions (drug delivery systems)
Synergistic drug interactions
Tablets (drug delivery systems)
Topical drug delivery systems
(RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)

IT Steroid receptors
Thyroid hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TR (thyroid/steroid hormone receptor), ligands; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)

IT Keratosis
(actinic; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)

IT Dermis
(atrophy; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)

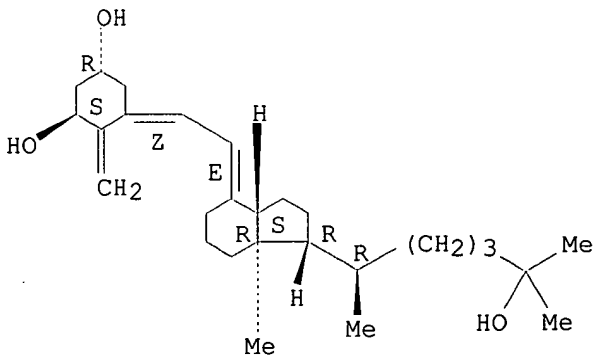
IT Inflammation
(cellulitis; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)

IT Skin diseases
(epidermis, atrophy; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)

IT Peroxisome proliferator-activated receptors
Retinoic acid receptors
Retinoid X receptors
Thyroid hormone receptors
Vitamin D receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ligands; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor

superfamily)
IT Skin diseases
(scar; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)
IT Sebaceous gland
(sebaceous function disorder; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)
IT Drug delivery systems
(systemic; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)
IT 302-79-4, all-trans-Retinoic acid 19356-17-3, 25-Hydroxyvitamin D3 **32222-06-3**, 1.alpha.,25-Dihydroxyvitamin D3 **41294-56-8**, 1.alpha.-Hydroxyvitamin D3 **60133-18-8**, 1.alpha.,25-Dihydroxyvitamin D2 94497-51-5 102121-60-8 104224-10-4 **124043-51-2**, 1.alpha.,24-Dihydroxyvitamin D2 153559-46-7 156691-84-8 186793-20-4
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)
IT **1406-16-2**, Vitamin D 6893-02-3, Triiodothyronine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptors, ligands; RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)
IT **32222-06-3**, 1.alpha.,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(RXR receptor-specific ligands for therapeutic and cosmetic use in conjunction with ligands of the steroid/thyroid receptor superfamily)
RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

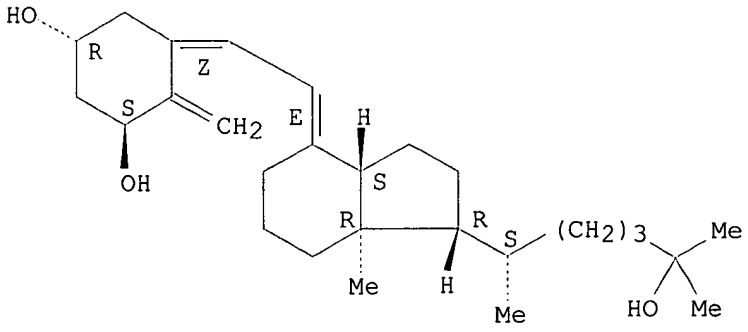
Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 18 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:25532 HCAPLUS
DN 126:84413
TI Prevention of **type I diabetes** by late intervention with nonhypercalcemic analogs of vitamin D3 in combination with cyclosporin A
AU Casteels, K.; Waer, M.; Bouillon, R.; Allewaert, K.; Laureys, J.; Mathieu, C.
CS Laboratories Experimental Medicine and Endocrinology (LEGENDO), Catholic University Leuven, Louvain, 3000, Belg.

SO Transplant. Proc. (1996), 28(6), 3095
CODEN: TRPPA8; ISSN: 0041-1345
PB Appleton & Lange
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The authors evaluated the protective potential of potent analog of vitamin D3 MC1288 (20 epi-1,25-dihydroxyvitamin D3) alone or in combination with a short induction course of cyclosporin A in NOD mice who already show active .beta.-cell destruction, demonstrated by the presence of insulitis in pancreatic biopsies. Treatment with MC1288 did not decrease diabetes incidence, but the combination therapy decreased diabetes incidence to 30%. All treatment regimens were well tolerated, although no immunosuppression was obsd.
ST diabetes prevention vitamin D3 analog cyclosporin
IT **Antidiabetic** agents
Drug interactions
(prevention of **type I diabetes** by late intervention with nonhypercalcemic analogs of vitamin D3 in combination with cyclosporin A)
IT 59865-13-3, Cyclosporin A **134523-84-5**, MC1288
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prevention of **type I diabetes** by late intervention with nonhypercalcemic analogs of vitamin D3 in combination with cyclosporin A)
IT **134523-84-5**, MC1288
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prevention of **type I diabetes** by late intervention with nonhypercalcemic analogs of vitamin D3 in combination with cyclosporin A)
RN 134523-84-5 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 19 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:342975 HCAPLUS
DN 125:26330
TI Vitamin D analogs in **insulin**-dependent **diabetes mellitus** and other autoimmune diseases: A therapeutic perspective
AU Mauricio, Didac; Mandrup-Poulsen, Thomas; Nerup, Joern
CS Steno Diabetes Center, Gentofte, Den.
SO Diabetes/Metab. Rev. (1996), 12(1), 57-68
CODEN: DMREEG; ISSN: 0742-4221
DT Journal; General Review
LA English

or Ined 10-1-01

CC 2-0 (Mammalian Hormones)
AB A review, with 87 refs., on the application of vitamin D derivs. in the prevention and treatment of autoimmune diseases, with special ref. to **insulin**-dependent **diabetes mellitus**.
ST review vitamin D analog autoimmune disease; **diabetes mellitus** vitamin D analog review
IT Autoimmune disease
(vitamin D analogs in treatment of **insulin**-dependent **diabetes mellitus** and other autoimmune diseases in humans)
IT Immunity
(vitamin D and immune system)
IT **Diabetes mellitus**
(**insulin**-dependent, vitamin D analogs in treatment of **insulin**-dependent **diabetes mellitus** and other autoimmune diseases in humans)
IT **1406-16-2D**, Vitamin D, analogs **32222-06-3**, 1.alpha.,25-Dihydroxyvitamin D3
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(vitamin D analogs in treatment of **insulin**-dependent **diabetes mellitus** and other autoimmune diseases in humans)
IT **1406-16-2D**, Vitamin D, analogs
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(vitamin D analogs in treatment of **insulin**-dependent **diabetes mellitus** and other autoimmune diseases in humans)
RN 1406-16-2 HCAPLUS
CN Vitamin D (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L81 ANSWER 20 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:124253 HCAPLUS
DN 124:251647
TI Treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**: The effect of 1.alpha.-hydroxyvitamin D3
AU Al-Qadreh, A.; Voskaki, I.; Kassiou, C.; Athanasopoulou, H.; Sarafidou, E.; Bartsocas, C. S.
CS Institute Child Health, "Ag. Sophia" Children's Hospital, Athens, GR-11527, Greece
SO Eur. J. Pediatr. (1996), 155(1), 15-17
CODEN: EJPEDT; ISSN: 0340-6199
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Twelve children (8 boys and 4 girls) with **insulin**-dependent **diabetes mellitus** (IDDM), aged 9-15 yr, received 1 .alpha.-hydroxyvitamin D3 (1.alpha.-OHD3) in a dose of 0.05 .mu.g/kg per day for 1 yr. Duration of disease varied between 2.8 and 9 yr. Bone d. was detd. in the distal third of forearm using single photon absorptiometry, and was expressed as std. scores with respect to sex- and age-matched controls. Bone d. measurements and ultrasound studies of the kidneys were performed at 0, 6 and 12 mo. Serum Ca, ionized Ca, P, Mg, creatinine, alk. phosphatase, glycosylated Hb in morning blood samples and urinary Ca, P, Mg, and hydroxyproline were regularly detd. One patient was excluded from the study because of hypercalciuria and one because of lack of compliance. Bone d. increased significantly after 6 and 12 mo of 1.alpha.-OHD3 administration. None of the biochem. parameters changed significantly. Evidently, osteopenia is not uncommon in children and adolescents with IDDM. In 10 children with IDDM and osteopenia the administration of 1.alpha.-OHD3 for 1 yr cor. bone loss.
ST hydroxyvitamin D3 osteopenia diabetes child
IT Blood serum
Urine

(blood serum and urinary parameters in hydroxyvitamin D3 treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

IT Hemoglobins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(glycosylated; blood serum and urinary parameters in hydroxyvitamin D3 treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

IT Sex
(hydroxyvitamin D3 in treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

IT Developmental stages
(child, hydroxyvitamin D3 in treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

IT **Diabetes mellitus**
(juvenile, hydroxyvitamin D3 in treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

IT Bone, disease
(osteopenia, hydroxyvitamin D3 in treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

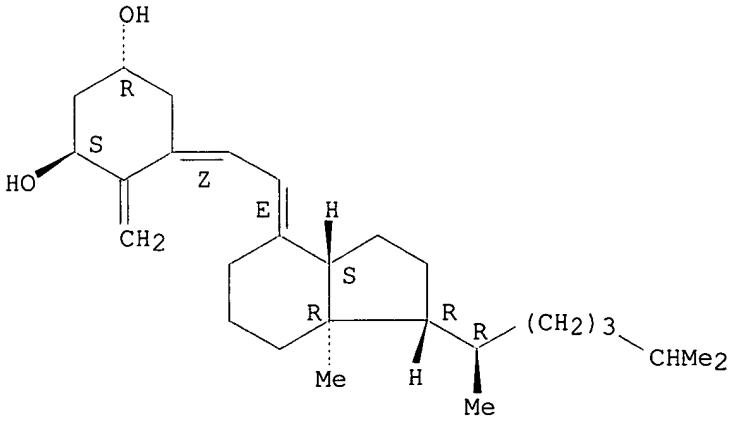
IT 51-35-4, Hydroxyproline 60-27-5, Creatinine 7439-95-4, Magnesium, biological studies 7440-70-2, Calcium, biological studies 7723-14-0, Phosphorus, biological studies 9001-78-9
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(blood serum and urinary parameters in hydroxyvitamin D3 treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

IT **41294-56-8**, 1.alpha.-Hydroxyvitamin D3
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(hydroxyvitamin D3 in treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

IT **41294-56-8**, 1.alpha.-Hydroxyvitamin D3
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(hydroxyvitamin D3 in treatment of osteopenia in children with **insulin**-dependent **diabetes mellitus**)

RN 41294-56-8 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3-diol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

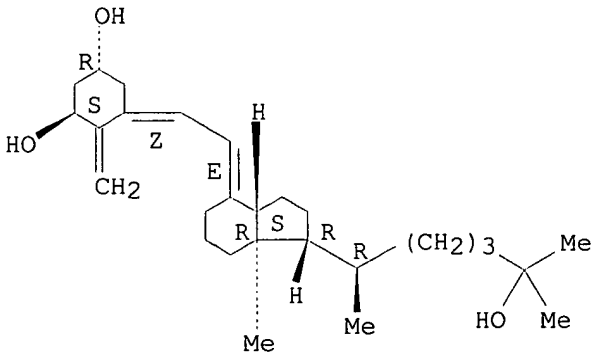
Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



L81 ANSWER 21 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:706199 HCAPLUS
DN 123:161608
TI Prevention of **type I diabetes** in NOD mice by 1,25 dihydroxyvitamin D3 and its analogs
AU Mathieu, Chantal; Waer, Mark; Bouillon, Roger

CS Laboratory Experimental Medicine and Endocrinology (LEGENDO), Catholic University Leuven, Belg.
SO Proc. Workshop Vitam. D (1994), 9th(Vitamin D), 540-8
CODEN: PWVDDU; ISSN: 0721-7110
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Studies were carried out to evaluate the effects of 1,25 dihydroxyvitamin D3 on the incidence of clin. diabetes in the NOD mouse, to investigate its effects on the immune system, and to study the effects of two structural analogs (Ro24-2673 and MC903) on the prevention of insulitis in this model.
ST dihydroxyvitamin D3 analog antidiabetic immunomodulator
IT Immunomodulators
(dihydroxyvitamin D3 and its analogs prevention of **type I diabetes** and effect on immune system)
IT **Antidiabetics and Hypoglycemics**
(**type I**; dihydroxyvitamin D3 and its analogs prevention of **type I diabetes** and effect on immune system)
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3 **112965-21-6**, MC903 124409-58-1
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 and its analogs prevention of **type I diabetes** and effect on immune system)
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 and its analogs prevention of **type I diabetes** and effect on immune system)
RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 22 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:546780 HCAPLUS
DN 122:291321
TI Preparation of novel vitamin D **analogs** as drugs.
IN Grue-Soerensen, Gunner
PA Leo Pharmaceutical Products Lts. A/S, Den.
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59

CC 32-7 (Steroids)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9502577	A1	19950126	WO 1994-DK271	19940701
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2162040	AA	19950126	CA 1994-2162040	19940701
	AU 9471829	A1	19950213	AU 1994-71829	19940701
	AU 690564	B2	19980430		
	EP 708755	A1	19960501	EP 1994-920900	19940701
	EP 708755	B1	19980422		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	CN 1125941	A	19960703	CN 1994-192588	19940701
	CN 1048241	B	20000112		
	JP 08512327	T2	19961224	JP 1994-504295	19940701
	AT 165346	E	19980515	AT 1994-920900	19940701
	ES 2117281	T3	19980801	ES 1994-920900	19940701
	RU 2130926	C1	19990527	RU 1996-102611	19940701
	US 5716945	A	19980210	US 1995-545762	19951107
	FI 9506108	A	19951219	FI 1995-6108	19951219
PRAI	GB 1993-14400	A	19930712		
	WO 1994-DK271	W	19940701		

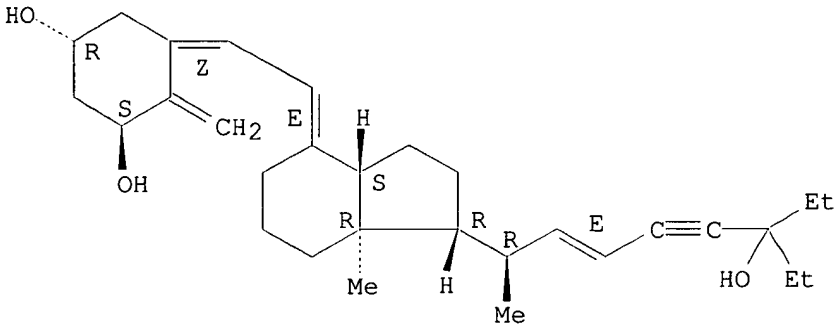
OS CASREACT 122:291321; MARPAT 122:291321
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. (I; X = H, OH; R1, R2 = H, hydrocarbyl; R1R2C = C3-8 carbocyclic ring; Q = single bond, C1-4 hydrocarbylene; R1, R2 and/or Q may be optionally substituted with .gtoreq.1 F atoms) and prodrugs thereof in which .gtoreq.1 of the OH groups are masked as groups which can be reconverted to OH groups in vivo, were prepd. Thus, 1(S),3(R)-dihydroxy-20(R)-(5-ethyl-5-hydroxyhept-1(E)-en-3-yn-1-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene, prepd. from aldehyde 20(S)-(II), showed superior antiproliferative activity in U937 leukemia cells (score of 89, vs. 1 for calcipotriol and 1.alpha.,25(OH)2 D3 in the test of Binderup and Bramm) while showing reduced calciuric effect relative to 1.alpha.,25(OH)2 D3.
ST vitamin d analog prepn drug; osteogenesis promoter vitamin d analog
IT Bone
(osteogenesis promoters; prepn. of novel vitamin D analogs as drugs)
IT **Antidiabetics and Hypoglycemics**
Antihypertensives
Immunomodulators
Inflammation inhibitors
(prepn. of novel vitamin D analogs as drugs)
IT Animal cell
(treatment of abnormal proliferation and/or differentiation; prepn. of novel vitamin D analogs as drugs)
IT Acne
Alopecia
Autoimmune disease
Hyperparathyroidism
Osteoporosis
Psoriasis
(treatment; prepn. of novel vitamin D analogs as drugs)
IT Skin, disease
(aging, treatment; prepn. of novel vitamin D analogs as drugs)
IT Inflammation inhibitors

(antiarthritics, prepn. of novel vitamin D analogs as drugs)
IT Skin, disease
(atrophy, treatment; prepn. of novel vitamin D analogs as drugs)
IT **163005-56-9P 163060-90-0P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel vitamin D analogs as drugs)
IT 112828-13-4 115648-67-4 163005-62-7
RL: RCT (Reactant)
(prepn. of novel vitamin D analogs as drugs)
IT 163005-57-0P 163005-58-1P 163005-59-2P 163005-60-5P 163005-61-6P 163060-91-1P 163060-92-2P 163060-93-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of novel vitamin D analogs as drugs)
IT **163005-56-9P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel vitamin D analogs as drugs)
RN 163005-56-9 HCAPLUS
CN 1,3-Cyclohexanediol, 5-[(2E)-[(1R,3aS,7aR)-1-[(1R,2E)-6-ethyl-6-hydroxy-1-methyl-2-octen-4-ynyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 23 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:394018 HCAPLUS
DN 122:152249
TI Prevention of **type I diabetes** in NOD mice by nonhypercalcemic doses of a new structural analog of 1,25-dihydroxyvitamin D3, KH1060
AU Mathieu, Chantal; Waer, Mark; Casteels, Kristina; Laureys, Jos; Bouillon, Roger
CS Laboratory for experimental medicine and endocrinology, Catholic University of Leuven, Leuven, Belg.
SO Endocrinology (1995), 136(3), 866-72
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Pharmacol. amts. of 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] have potent immunoregulatory activity, but with marked effects on calcium and bone metab. In this study we demonstrate that nonhypercalcemia-inducing nondemineralizing doses of an analog of 1,25-(OH)2D3, 1.alpha.,25-(OH)2-20-epo-22-oxa-24,26,27-trishomo-vitamin D (KH1060), can prevent **type I diabetes**. Female NOD mice received 1,25-(OH)2D3 (5 .mu.g/kg), KH1060 (0.4 or 0.2 .mu.g/kg), or the treatment vehicle i.p. every 2 days from 21-200 days of age. The incidence of **diabetes**

in controls was 17 of 31 (55%), whereas 7 of 38 (18%) 1,25-(OH)2D3-treated mice, 3 of 27 (11%) KH1060 (0.4 .mu.g/kg)-treated mice, and 6 of 27 (22%) KH1060 (0.2 .mu.g/kg)-treated mice developed **diabetes**. Protection was achieved with the low KH1060 dose without effects on calcium or bone metab., as evaluated by serum calcium (9.5 vs. 9.4 mg/dL in controls), serum osteocalcin (82 vs. 83 ng/mL), bone calcium content (6.8 vs. 6.4 mg/tibia), urinary calcium (21 vs. 21 mg/dL), pyridinoline excretion, and duodenal calbindin-D9K concn. The proposed mechanism of action is a restoration of suppressor cell activity, as demonstrated in vitro (suppressor cell assay) and in vivo (cell transfer expts.). This study demonstrates that an analog of 1,25-(OH)2D3 prevents **type I diabetes** in NOD mice without significant effects on calcium or bone metab.

ST diabetes prevention dihydroxyvitamin D3 analog; KH 1060 diabetes prevention

IT Bone
(calcium and bone metab. in **diabetes type I** prevention by hydroxyvitamin D3 analog KH 1060)

IT **Diabetes mellitus**
(juvenile, **diabetes type I** prevention by hydroxyvitamin D3 analog KH 1060)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(calcium and bone metab. in **diabetes type I** prevention by hydroxyvitamin D3 analog KH 1060)

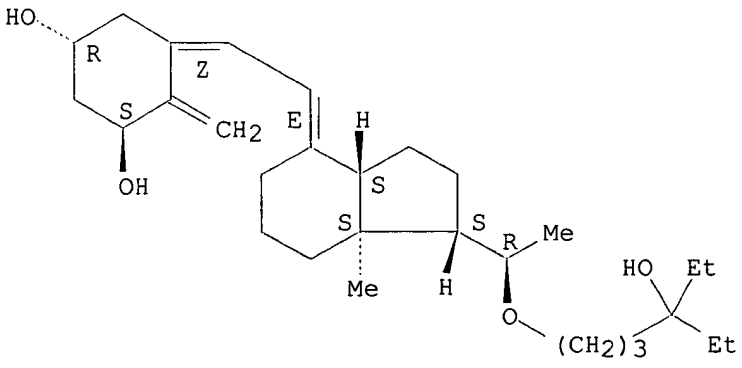
IT **131875-08-6**, KH 1060
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**diabetes type I** prevention by hydroxyvitamin D3 analog KH 1060)

IT **131875-08-6**, KH 1060
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**diabetes type I** prevention by hydroxyvitamin D3 analog KH 1060)

RN 131875-08-6 HCAPLUS

CN 1,3-Cyclohexanediol, 5-[(2E)-[(1S,3aS,7aS)-1-[(1R)-1-[(4-ethyl-4-hydroxyhexyl)oxy]ethyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 24 OF 39 HCAPLUS COPYRIGHT 2001 ACS

AN 1995:379275 HCAPLUS

DN 122:157682

TI Osteopenia in genetically diabetic DB/DB mice and effects of 1.alpha.-hydroxyvitamin D3 on the osteopenia

AU Takeshita, Nobuaki; Mutoh, Seitaro; Yamaguchi, Isamu

CS Basic Res. Group, Tsukuba Res. Labs., Ibaraki, 300-26, Japan

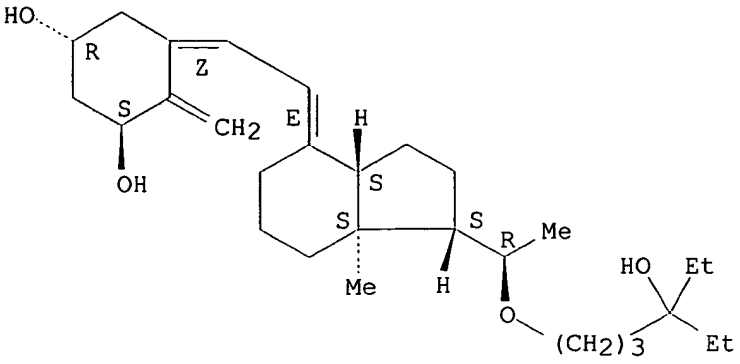
SO Life Sci. (1995), 56(13), 1095-101
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
CC 14-8 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 1
AB To explore the pathogenesis of non-**insulin**-dependent **diabetes mellitus** assocd. osteopenia, we examd. age-related changes of the femur metaphyseal bone mineral d. in genetically **diabetic** (db/db) mice and non-**diabetic** (+/+) mice of the same strain using single photon absorptiometry and characterized the osteopenia pharmacol. and biochem. Bone mineral d. increased with age in the +/+ mice from 5 to 16 wk of age, but reached a plateau in the db/db mice at 8 wk of age, and significant differences between the two groups were obsd. after 12 wk of age. Ash wt. (A) and dry wt. (D) of the femur and A/D ratio were significant lower in the db/db mice than in the +/+ mice after 8 wk of age. Significant elevations of serum calcium and parathyroid hormone (PTH) were obsd. after 8 wk and 12 wk of age, resp. Serum 1.alpha.,25-dihydroxyvitamin D levels were significantly decreased in the db/db mice compared to the +/+ mice. Daily oral treatment with 1.alpha.-hydroxyvitamin D3 (1.alpha.-(OH)D3) for 4 wk starting from 8 wk of age significantly attenuated the bone loss in the db/db mice. These results suggest that an impaired bone mineralization probably by insufficient vitamin D activity and high PTH levels are involved in the osteopenia in the db/db mice. 1.alpha.-(OH)D3 exerted beneficial effects on the bone loss.
ST vitamin D osteopenia diabetes
IT **Diabetes mellitus**
(non-**insulin**-dependent, pathogenesis of non-**insulin**-dependent **diabetes mellitus** assocd. osteopenia and effect of 1.alpha.-hydroxyvitamin D3 on bone loss using **diabetic** db/db mice)
IT Bone, disease
(osteopenia, pathogenesis of non-**insulin**-dependent **diabetes mellitus** assocd. osteopenia and effect of 1.alpha.-hydroxyvitamin D3 on bone loss using **diabetic** db/db mice)
IT **1406-16-2**, Vitamin d
RL: ADV (Adverse effect, including toxicity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(deficiency of vitamin D in non-**insulin**-dependent **diabetes mellitus** assocd. osteopenia)
IT **41294-56-8**, 1.alpha.-Hydroxyvitamin D3
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(effect of 1.alpha.-hydroxyvitamin D3 on osteopenia in diabetic db/db mice)
IT 9002-64-6, Parathyroid hormone
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(elevation of parathyroid hormone in non-**insulin**-dependent **diabetes mellitus** assocd. osteopenia)
IT **1406-16-2**, Vitamin d
RL: **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(deficiency of vitamin D in non-**insulin**-dependent **diabetes mellitus** assocd. osteopenia)
RN 1406-16-2 HCAPLUS
CN Vitamin D (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L81 ANSWER 25 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:345285 HCAPLUS
DN 122:122708
TI Prevention of autoimmune destruction of transplanted **islets** in spontaneously **diabetic** NOD mice by KH1060, a 20-epi

analog of vitamin D: synergy with cyclosporine
AU Mathieu, C.; Laureys, J.; Waer, M.; Bouillon, R.
CS Laboratory for Experimental Medicine and Endocrinology, K.U. Leuven, Louvain, 3000, Belg.
SO Transplant. Proc. (1994), 26(6), 3128-9
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal
LA English
CC 1-7 (Pharmacology)
AB The aim of the present study was to evaluate the capacity of KH1060, a potent structural analog of 1,25(OH)2D3, to prevent autoimmune disease recurrence after islet transplantation both in monotherapy and in combination with cyclosporine (CyA). It was demonstrated that KH1060, given in high (1 .mu.g/kg/2 days) doses can delay autoimmune disease recurrence after syngeneic islet transplantation in NOD mice. These doses are, however, toxic, due in part to hypercalcemia. The combination of nontoxic subtherapeutic doses of KH1060 (0.5 .mu.g/2 days) and subtherapeutic doses of CyA synergistically prevented recurrence of autoimmune diabetes and reinstalled tolerance after syngeneic islet transplantation in NOD mice. Therefore, it is proposed that KH1060 or other new noncalcemic analogs of I,25(OH)2D3 may possibly be used as dose-reducing agents for classical immunosuppressive drugs such as CyA, FK 506, and rapamycin. In this manner, the structural analogs of 1,25(OH)2D3 could be the future corticosteroid replacement drugs, thus avoiding many side effects in organ transplantation and other diseases requiring immunosuppression.
ST KH1060 cyclosporine islet transplantation synergistic interaction; immunosuppressant cyclosporine islet transplantation KH1060
IT Immunosuppressants
Transplant and Transplantation
(prevention of autoimmune destruction of transplanted islets by vitamin D analog KH1060 and synergy with cyclosporine)
IT Drug interactions
(synergistic, prevention of autoimmune destruction of transplanted islets by vitamin D analog KH1060 and synergy with cyclosporine)
IT **Pancreatic islet of Langerhans**
(transplant, prevention of autoimmune destruction of transplanted islets by vitamin D analog KH1060 and synergy with cyclosporine)
IT 59865-13-3, Cyclosporin A **131875-08-6**, KH1060
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prevention of autoimmune destruction of transplanted islets by vitamin D analog KH1060 and synergy with cyclosporine)
IT **131875-08-6**, KH1060
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prevention of autoimmune destruction of transplanted islets by vitamin D analog KH1060 and synergy with cyclosporine)
RN 131875-08-6 HCAPLUS
CN 1,3-Cyclohexanediol, 5-[(2E)-[(1S,3aS,7aS)-1-[(1R)-1-[(4-ethyl-4-hydroxyhexyl)oxy]ethyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

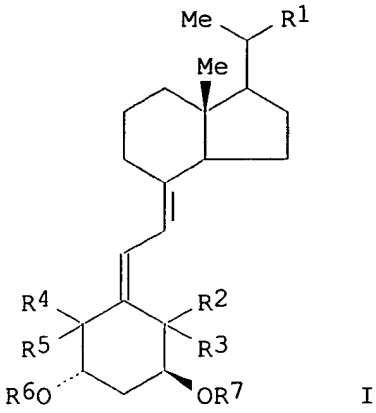
Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 26 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1995:231165 HCAPLUS
DN 122:10367
TI Preparation of 22-thia-vitamin D **analogs** as drugs
IN Grue-Soerensen, Gunnar; Ottosen, Erik Rytter
PA Leo Pharmaceutical Products Ltd. A/S, Den.
SO PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59
CC 32-7 (Steroids)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9414766	A1	19940707	WO 1993-DK425	19931217
	W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2146775	AA	19940707	CA 1993-2146775	19931217
	AU 9458087	A1	19940719	AU 1994-58087	19931217
	AU 668638	B2	19960509		
	EP 675878	A1	19951011	EP 1994-903741	19931217
	EP 675878	B1	19970129		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 08504775	T2	19960521	JP 1993-514697	19931217
	AT 148454	E	19970215	AT 1994-903741	19931217
	ES 2098123	T3	19970416	ES 1994-903741	19931217
	RU 2136660	C1	19990910	RU 1995-113480	19931217
	US 5554599	A	19960910	US 1995-411634	19950411
	FI 9502972	A	19950616	FI 1995-2972	19950616
PRAI	GB 1992-26877	A	19921223		
	WO 1993-DK425	W	19931217		

OS MARPAT 122:10367
GI



I

AB Title compds. (I; R1 = YZCR2OH; R = alkyl; R2R3 = CH2; R4-R7 = H; Y = SO0-2; Z = hydrocarbylene) were prepd. as antiinflammatories, immunomodulators, and cell proliferation inhibitors (no data). Thus, (20S)-I (R2 = R3 = H, R4R5 = CH2, R6 = R7 = SiMe2CMe3)[(20S)-II; R = CHO] was converted in 3 steps to (20S)- and (20R)-II (R = SH) which mixt. was S-alkylated by Br(CH2)3CEt2OSiMe3 and the products isomerized and deprotected to give (20S)- and (20R)-I [R1 = S(CH2)3CEt2OH, R2R3 = CH2, R4-R7 = H].

ST vitamin D thia prepn drug; antiinflammatory thiavitamin D prepn; immunomodulator thiavitamin D prepn; cell proliferation inhibitor thiavitamin D

IT Skin, disease
(ageing, treatment of, thiavitamin D analogs for)

IT Bone
(formation of, promotion of, thiavitamin D analogs for)

IT **Antidiabetics and Hypoglycemics**
Antihypertensives
Immunomodulators
Inflammation inhibitors
(thiavitamin D analogs)

IT Acne
Alopecia
Autoimmune disease
Hyperparathyroidism
Osteoporosis
Psoriasis
(treatment of, thiavitamin D analogs for)

IT Inflammation inhibitors
(antiarthritics, thiavitamin D analogs)

IT Bronchodilators
(antiasthmatics, thiavitamin D analogs)

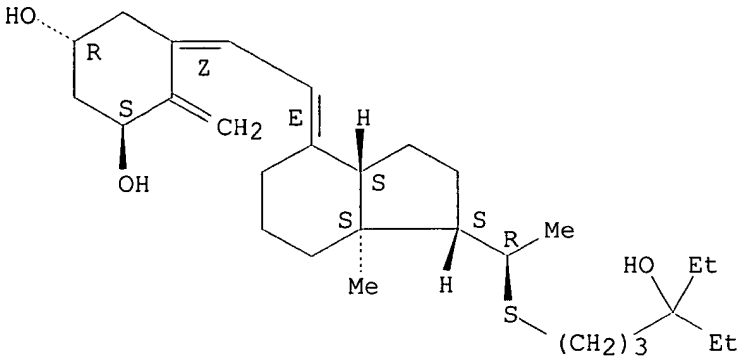
IT Skin, disease
(atrophy, steroid-induced, treatment of, thiavitamin D analogs for)

IT 159527-40-9P 159527-41-0P 159527-42-1P 159527-43-2P 159527-44-3P
159527-45-4P 159527-46-5P 159527-47-6P 159527-48-7P 159527-49-8P
159527-50-1P 159527-51-2P 159527-52-3P 159527-53-4P 159527-54-5P
159527-55-6P 159527-56-7P 159527-57-8P 159527-58-9P 159527-59-0P
159527-60-3P 159527-61-4P 159527-62-5P 159527-63-6P 159527-64-7P
159527-65-8P 159573-93-0P 159573-94-1P 159573-95-2P 159573-96-3P
159573-97-4P 159573-98-5P 159573-99-6P 159574-00-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of drug)

IT **159527-36-3P 159527-37-4P 159527-38-5P**
159527-39-6P 159573-89-4P 159573-90-7P
159573-91-8P 159573-92-9P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of, as drug)
IT 67883-17-4 112828-13-4 128312-85-6 128313-07-5 159527-66-9
RL: RCT (Reactant)
(reaction of, in prepn. of drug)
IT **159527-36-3P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)
RN 159527-36-3 HCAPLUS
CN 1,3-Cyclohexanediol, 5-[[1-[1-[(4-ethyl-4-hydroxyhexyl)thio]ethyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, [1S-[1.alpha.(S*),3a.beta.,4E(1S*,3R*,5Z),7a.alpha.]]- (9CI) (CA INDEX NAME)

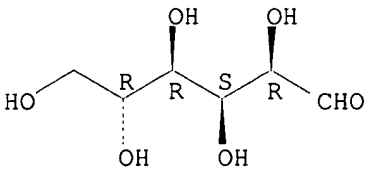
Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 27 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:647083 HCAPLUS
DN 121:247083
TI Effects of 1,25-dihydroxyvitamin D3 and the analogs MC903 and KH1060 on interleukin-1.beta.-induced inhibition of rat pancreatic islet .beta.-cell function in vitro
AU Sandler, Stellan; Buschard, Karsten; Bendtzen, Klaus
CS Dep. Medical Cell Biology, Uppsala Univ., Uppsala, Germany
SO Immunol. Lett. (1994), 41(1), 73-7
CODEN: IMLED6; ISSN: 0165-2478
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The cytokine interleukin-1.beta. (IL-1.beta.) has been proposed to be involved in pancreatic .beta.-cell destruction during the development of autoimmune **insulin**-dependent **diabetes mellitus**. It has been demonstrated that 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) inhibits T-lymphocyte and monocyte functions in vitro, probably through an effect on cytokine actions, and that in vivo treatment with vitamin D can prevent pancreatic insulitis in **diabetes**-prone NOD mice. In this study isolated rat pancreatic islets were exposed to human IL-1.beta. (125 U/mL) in the absence or presence of 1,25-(OH)2D3 or the analogs MC903 and KH1060 for 48-72 h in tissue culture, whereupon medium **insulin** accumulation, islet DNA and **insulin** contents, glucose-stimulated **insulin** secretion and glucose oxidn. rates were assessed. All three vitamin D derivs. countered the suppressive effect of IL-1.beta. on medium **insulin** accumulation, 1,25-(OH)2D3 being active at concns. down to 0.1 nM, i.e., 1-2 orders of magnitude more efficacious than the analogs. However, only KH1060 opposed the suppressive effect of IL-1.beta. on islet glucose-stimulated **insulin** secretion and glucose oxidn. rate despite the fact that KH1060 itself reduced the islet DNA and **insulin** content by approx. 10% and 30%, resp. The protective effect obsd. against IL-1.beta.-induced .beta.-cell dysfunction

might be related to a beneficial action of vitamin D3 on the mitochondrial calcium metab. of the .beta.-cells.
ST dihydroxyvitamin D3 interleukin pancreatic islet; MC903 KH1060 interleukin insulin secretion glucose
IT Lymphokines and Cytokines
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(interleukin 1.beta., protective effects of dihydroxyvitamin D3 and analogs on interleukin-1.beta.-induced inhibition of rat pancreatic islet .beta.-cell function in vitro)
IT **Pancreatic islet of Langerhans**
(.beta.-cell, protective effects of dihydroxyvitamin D3 and analogs on interleukin-1.beta.-induced inhibition of rat pancreatic islet .beta.-cell function in vitro)
IT **50-99-7**, D-Glucose, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(dihydroxyvitamin D3 and analogs effect on IL-1 suppressive effect on islet glucose-stimulated insulin secretion and glucose oxidn.)
IT **9004-10-8**, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(dihydroxyvitamin D3 and analogs effect on IL-1 suppressive effect on islet glucose-stimulated insulin secretion and glucose oxidn.)
IT **32511-63-0**, 1,25-Dihydroxyvitamin D3 **112965-21-6**, MC903
131875-08-6, KH1060
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(protective effects of dihydroxyvitamin D3 and analogs on interleukin-1.beta.-induced inhibition of rat pancreatic islet .beta.-cell function in vitro)
IT **50-99-7**, D-Glucose, biological studies
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**
(dihydroxyvitamin D3 and analogs effect on IL-1 suppressive effect on islet glucose-stimulated insulin secretion and glucose oxidn.)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L81 ANSWER 28 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1994:571317 HCAPLUS
DN 121:171317
TI Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D3
AU Mathieu, C.; Waer, M.; Laureys, J.; Rutgeerts, O.; Bouillon, R.
CS Lab. Exp. Med. Endocrinol., Cathol. Univ. Leuven, Louvain, Belg.
SO Diabetologia (1994), 37(6), 552-8
CODEN: DBTGAJ; ISSN: 0012-186X
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
ordered 10-1-01
AB 1,25-Dihydroxyvitamin D3, the active form of vitamin D, has immunomodulatory properties in vitro and in vivo. Treatment with 1,25-dihydroxyvitamin D3 (5 .mu.g/kg on alternate days) prevented the development of clin. diabetes in NOD mice, an animal model of human autoimmune diabetes. Diabetes incidence in female NOD mice at the age of 200 days was reduced to 8% in the 1,25-dihydroxyvitamin D3-treated group vs. 56% in the control group. In parallel, treatment with

1,25-dihydroxyvitamin D3 resulted in a complete normalization of the capacity to induce suppressor mechanisms in an autologous MLR, which is severely depressed in control NOD mice. The existence of such suppressor cells was confirmed in transfer expts., whereby cotransfer of splenocytes from 1,25-dihydroxyvitamin D3-treated NOD mice prevented diabetes transfer by splenocytes from diabetic NOD mice into irradiated, 6-8-wk-old male NOD mice. Other known immune defects of the NOD mice, such as defective natural killer cell killing of YAC-1 targets and defective thymocyte activation by anti-CD3 were not cor. The pharmacol. doses of 1,25-dihydroxyvitamin D3 were universally well tolerated as reflected by a normal wt. gain of the mice. Serum calcium was increased (2.5 vs. 2.2 mmol/L in the control group), whereas osteocalcin levels nearly doubled and bone calcium content was halved. These findings show that 1,25-dihydroxyvitamin D3 can prevent diabetes in NOD mice, probably through the correction of their defective suppressor function.

ST dihydroxyvitamin D3 autoimmune diabetes

IT **Antidiabetics and Hypoglycemics**
(autoimmune diabetes prevention by dihydroxyvitamin D3)

IT Bone
(bone calcium and osteocalcin response to dihydroxyvitamin D3 in autoimmune diabetes)

IT Blood serum
(serum calcium and osteocalcin response to dihydroxyvitamin D3 in autoimmune diabetes)

IT Osteocalcins
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(serum calcium and osteocalcin response to dihydroxyvitamin D3 in autoimmune diabetes)

IT **Diabetes mellitus**
(autoimmune, serum calcium and osteocalcin response to dihydroxyvitamin D3 in autoimmune **diabetes**)

IT Lymphocyte
(suppressor cell, autoimmune diabetes prevention by dihydroxyvitamin D3)

IT **32222-06-3**, 1.alpha.,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(autoimmune diabetes prevention by dihydroxyvitamin D3)

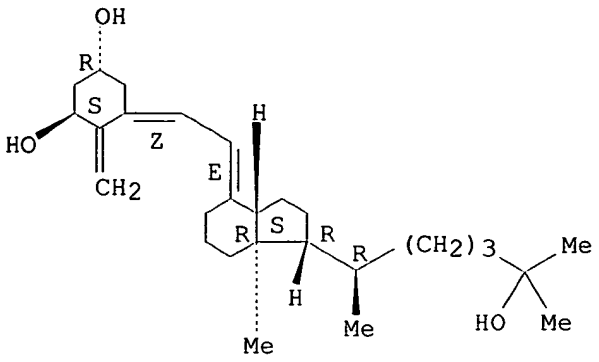
IT 7440-70-2, Calcium, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(serum calcium and osteocalcin response to dihydroxyvitamin D3 in autoimmune diabetes)

IT **32222-06-3**, 1.alpha.,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(autoimmune diabetes prevention by dihydroxyvitamin D3)

RN 32222-06-3 HCAPLUS

CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 29 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1992:449008 HCAPLUS
DN 117:49008
TI Preparation of vitamin D analogs as drugs
IN Calverley, Martin John; Grue-Soerensen, Gunnar; Binderup, Ernst Torndal
PA Leo Pharmaceutical Products Ltd. A/S, Den.
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59
CC 32-5 (Steroids)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9115475	A1	19911017	WO 1991-DK91	19910322
	W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
	CA 2073983	AA	19911001	CA 1991-2073983	19910322
	AU 9175892	A1	19911030	AU 1991-75892	19910322
	AU 630804	B2	19921105		
	EP 522013	A1	19930113	EP 1991-907179	19910322
	EP 522013	B1	19941123		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05505613	T2	19930819	JP 1991-506764	19910322
	ES 2066434	T3	19950301	ES 1991-907179	19910322
	US 5374629	A	19941220	US 1992-910025	19920723
PRAI	GB 1990-7236		19900330		
	WO 1991-DK91		19910322		

OS MARPAT 117:49008
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. (I; X = H, OH; Y = O, S. SO, SO2; R1, R2 = H, hydrocarbyl; R1R2C = carbocyclyl; Q = hydrocarbylene; R3 = H, hydrocarbyl; R1, R2, Q may be substituted with D, F; n = 0, 1), and acylated or glycosylated derivs., were prepd. for treatment of cancer, psoriasis, autoimmune disease, hyperparathyroidism, diabetes, skin aging, graft rejection, etc. (no data). Thus, aldehyde II was successively reduced with NaBH4, alkylated with BrCH2CH2CH2CMe2OSiMe3/KOCMe3/18-crown-6 and photoisomerized with anthracene and Et3N in CH2Cl2 using a high pressure Hg lamp followed by desilylation with HF in MeCN/H2O to give I [R1 = R2 = Me, R3 = H, X =

OH, Y = O, Q = (CH2)3, n = 1] (III). Capsules and creams were prepd. contg. III.

ST vitamin D analog prepn drug; neoplasm inhibitor vitamin D analog; psoriasis treatment vitamin D analog; hyperparathyroidism treatment vitamin D analog; autoimmune disorder treatment vitamin D; antihypertensive vitamin D analog

IT Autoimmune disease
Diabetes mellitus
Hyperparathyroidism
Psoriasis
(treatment of, vitamin D analogs for)

IT Antihypertensives
Immunomodulators
Inflammation inhibitors
Neoplasm inhibitors
(vitamin D analogs)

IT Acne
Alopecia
(vitamin D analogs for treatment of)

IT 9,10-Secosteroids
RL: SPN (Synthetic preparation); PREP (Preparation)
(vitamin D analogs, prepn. of, as drugs)

IT Skin, disease
(aging, treatment of, vitamin D analogs for)

IT Inflammation inhibitors
(antiarthritics, vitamin D analogs)

IT Bronchodilators
(antiasthmatics, vitamin D analogs)

IT Transplant and Transplantation
(graft-vs.-host reaction, treatment, of vitamin D analogs for)

IT **139137-05-6P 139137-06-7P 139137-07-8P**
139137-08-9P 139137-09-0P 139137-10-3P
139137-11-4P 139137-12-5P 139137-13-6P
139137-14-7P 139137-15-8P 139137-16-9P
139137-17-0P 139137-18-1P 139137-19-2P
139137-20-5P 139137-21-6P 139137-22-7P
139137-23-8P 139137-24-9P 139137-25-0P
139137-26-1P 139137-27-2P 139174-96-2P
139174-97-3P 139239-31-9P 139239-32-0P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)

IT 134404-89-0P 134404-90-3P 134523-95-8P 139137-28-3P 139137-29-4P
139137-30-7P 139137-31-8P 139137-32-9P 139137-33-0P 139137-34-1P
139137-35-2P 139137-36-3P 139137-37-4P 139137-38-5P 139137-39-6P
139137-40-9P 139137-41-0P 139174-98-4P 139174-99-5P 139175-00-1P
139175-01-2P 139175-02-3P 139175-03-4P 139175-04-5P 139175-05-6P
139175-06-7P 139175-07-8P 139175-08-9P 139175-09-0P 139175-10-3P
139175-11-4P 139175-12-5P 139175-13-6P 139175-14-7P 139175-19-2P
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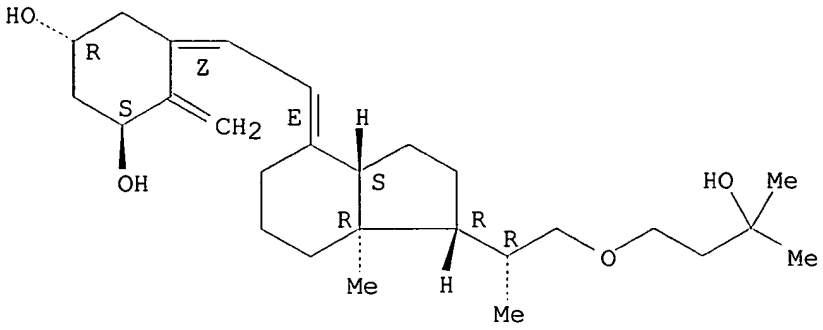
139239-38-6P 139240-80-5P 139240-81-6P 139240-82-7P 139240-83-8P
139240-84-9P 139240-85-0P 139240-86-1P 139240-87-2P 139240-88-3P
139240-89-4P 139240-90-7P 139240-91-8P 139240-92-9P 139240-93-0P
139240-94-1P 139240-95-2P 139342-61-3P 139342-62-4P 139342-63-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for vitamin D analog)

IT 67-64-1, 2-Propanone, reactions 96-22-0, 3-Pentanone 98-59-9
106-96-7 334-88-3 620-24-6 870-63-3 917-54-4 2948-47-2
3045-32-7 7446-09-5, Sulfur dioxide, reactions 7765-97-1 14967-17-0
17890-64-1 21378-06-3 33959-26-1 115648-67-4 128312-85-6
139175-15-8 139175-16-9 139175-17-0 139175-18-1
RL: RCT (Reactant)
(reaction of, in prepn. vitamin D analogs)

IT **139137-05-6P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of, as drug)
RN 139137-05-6 HCAPLUS
CN 1,3-Cyclohexanediol, 4-methylene-5-[(2E)-[(1R,3aS,7aR)-octahydro-1-[(1R)-2-(3-hydroxy-3-methylbutoxy)-1-methylethyl]-7a-methyl-4H-inden-4-ylidene]ethylidene]-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 30 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:450097 HCAPLUS
DN 115:50097
TI Preparation of novel vitamin D analogs
IN Binderup, Ernst Torndal; Calverley, Martin John
PA Leo Pharmaceutical Products Ltd. A/S, Den.
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59
CC 32-8 (Steroids)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9100855	A1	19910124	WO 1990-DK168	19900704
	W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
	ZA 9005094	A	19910424	ZA 1990-5094	19900629
	CA 2057048	AA	19910101	CA 1990-2057048	19900704
	AU 9061563	A1	19910206	AU 1990-61563	19900704
	AU 630227	B2	19921022		
	EP 482100	A1	19920429	EP 1990-911969	19900704
	EP 482100	B1	19941005		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	JP 04506965	T2	19921203	JP 1990-511187	19900704
	ES 2064749	T3	19950201	ES 1990-911969	19900704
	US 5190935	A	19930302	US 1991-773950	19911119
	FI 93724	B	19950215	FI 1991-6151	19911227
	FI 93724	C	19950526		
PRAI	GB 1989-15770		19890710		
	WO 1990-DK168		19900704		

OS MARPAT 115:50097
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Vitamin D analogs [I; R1, R2 = H, C1-8 hydrocarbyl, R1R2 = C3-8 carbocyclic residue; m = 0-4; n = 2,3], useful in the treatment and prophylaxis of autoimmune diseases (including **diabetes mellitus**), hypertension, acne, alopecia, rheumatoid arthritis, asthma, etc., are prepd. Redn. of ketone II (R3R4 = O) with NaBH4 is THF gave alc. II (R3 = H, R4 = OH), which was photoisomerized in MePh in the presence of anthracene and Et3N and hydrolyzed with Bu4N+ F-.3H2O at 60.degree. in the THF under N to give I (R1 = H, R2 = cyclopropyl, m = 0, n = 2). Also prepd. were 32 addnl. I. Capsule and dermatol. cream contg. I were given.

ST vitamin D analog prepn drug; autoimmune disease vitamin D analog; antihypertensive vitamin D analog; acne treatment vitamin D analog; alopecia treatment vitamin D analog; antiarthritic vitamin D analog; antiasthmatic vitamin D analog

IT Acne
Alopecia
Psoriasis
(treatment of, vitamin D analogs for)

IT **Antidiabetics and Hypoglycemics**
Inflammation inhibitors
Neoplasm inhibitors
(vitamin D analogs)

IT Inflammation inhibitors
(antiarthritics, vitamin D analogs)

IT Bronchodilators
(antiasthmatics, vitamin D analogs)

IT Disease
(autoimmune, treatment of, vitamin D analogs for)

IT 134404-37-8P 134404-38-9P 134404-39-0P 134404-40-3P 134404-41-4P
134404-42-5P 134404-43-6P 134404-44-7P 134425-76-6P 134523-38-9P
134523-39-0P 134523-40-3P 134523-41-4P 134523-42-5P 134523-43-6P
134523-44-7P 134523-45-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrolysis of, in prepn. of drugs)

IT 134404-28-7P 134404-29-8P 134404-30-1P 134404-31-2P 134404-32-3P
134404-33-4P 134404-34-5P 134404-35-6P 134404-36-7P 134523-36-7P
134523-37-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and photoisomerization of, in prepn. of drugs)

IT 112924-91-1P 134404-45-8P 134404-46-9P 134404-47-0P 134404-48-1P
134523-46-9P 134523-47-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of vitamin D analogs)

IT **134404-49-2P 134404-50-5P 134404-51-6P**
134404-52-7P 134404-53-8P 134404-54-9P
134404-55-0P 134404-56-1P 134404-57-2P
134404-58-3P 134404-59-4P 134404-60-7P
134523-48-1P 134523-49-2P 134523-50-5P
134523-51-6P 134523-52-7P 134523-53-8P
134523-54-9P 134676-91-8P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)

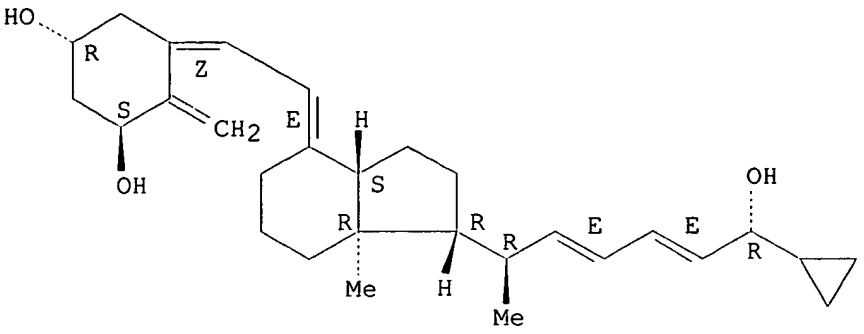
IT **1406-16-2DP**, Vitamin D, analogs
RL: PREP (Preparation)
(prepn. of, as drugs)

IT **134404-49-2P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)

RN 134404-49-2 HCAPLUS

CN 27-Nor-9,10-secocholesta-5,7,10(19),22,24-pentaene-1,3,26-triol, 26-cyclopropyl-, (1.alpha.,3.beta.,5Z,7E,22E,24E,26R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 31 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:428990 HCAPLUS
DN 115:28990
TI Preparation of vitamin D analogs
IN Calverley, Martin John; Binderup, Ernst Torndal
PA Leo Pharmaceutical Products Ltd. A/S, Den.
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59
CC 26-8 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9100271	A1	19910110	WO 1990-DK156	19900619
	W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
	CA 2051418	AA	19901230	CA 1990-2051418	19900619
	AU 9059637	A1	19910117	AU 1990-59637	19900619
	AU 629666	B2	19921008		
	EP 479871	A1	19920415	EP 1990-910609	19900619
	EP 479871	B1	19930421		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	JP 04506351	T2	19921105	JP 1990-509936	19900619
	AT 88465	E	19930515	AT 1990-910609	19900619
	ES 2055438	T3	19940816	ES 1990-910609	19900619
	ZA 9005043	A	19910529	ZA 1990-5043	19900628
	FI 93723	B	19950215	FI 1991-6150	19911227
	FI 93723	C	19950526		
	US 5401731	A	19950328	US 1993-113522	19930830
PRAI	GB 1989-14963		19890629		
	EP 1990-910609		19900619		
	WO 1990-DK156		19900619		
	US 1991-793417		19911024		

OS MARPAT 115:28990
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Vitamin D analogs I [R1, R2 = H, C1-8 hydrocarbyl, R1R2 = C3-8 carbocyclic residue; m = 0-7; n = 0, 1], useful in the treatment and prophylaxis of

autoimmune diseases (including **diabetes mellitus**), hypertension, acne, alopecia, rheumatoid arthritis, asthma, etc., are prepd. Redn. of ketone II (R3R4 = O) with NaBH4 gave alc. II (R3 = H, R4 = OH), which was photoisomerized in MePh in the presence of anthracene and Et3N and hydrolyzed with Bu4N+F-.3H2O at 60.degree. in THF under N to give I (R1 = H, R2 = cyclopropyl, m = 0, n = 1). Also prepd. were 18 addnl. I. Capsule and dermatol. cream formulations of I were given.

ST vitamin D analog prepn drug; autoimmune disease vitamin D analog; antihypertensive vitamin D analog prepn; acne treatment vitamin D analog; alopecia treatment vitamin D analog; antiarthritic vitamin D analog; antiasthmatic vitamin D analog

IT Acne
Alopecia
Psoriasis
(treatment of, vitamin D analogs for)

IT **Antidiabetics and Hypoglycemics**
Antihypertensives
Neoplasm inhibitors
(vitamin D analogs)

IT Inflammation inhibitors
(antiarthritics, vitamin D analogs)

IT Bronchodilators
(antiasthmatics, vitamin D analogs)

IT Disease
(autoimmune, treatment of, vitamin D analogs for)

IT 134404-92-5P 134404-93-6P 134404-94-7P 134404-95-8P 134425-78-8P
134523-69-6P 134523-70-9P 134523-71-0P 134523-72-1P 134523-73-2P
134523-74-3P 134523-75-4P 134523-76-5P 134523-77-6P 134523-78-7P
134523-79-8P 134523-80-1P 134523-81-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrolysis of)

IT 134404-83-4P 134404-84-5P 134404-85-6P 134404-86-7P 134404-87-8P
134404-88-9P 134404-89-0P 134404-90-3P 134404-91-4P 134523-60-7P
134523-61-8P 134523-62-9P 134523-63-0P 134523-64-1P 134523-65-2P
134523-66-3P 134523-67-4P 134523-68-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and photoisomerization of)

IT 67883-17-4P 83872-56-4P 128387-35-9P 134405-02-0P 134523-95-8P
134523-96-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of vitamin D analogs)

IT **134404-96-9P 134404-97-0P 134404-98-1P**
134404-99-2P 134405-00-8P **134405-01-9P**
134523-82-3P 134523-83-4P 134523-84-5P
134523-85-6P 134523-86-7P 134523-87-8P
134523-88-9P 134523-89-0P 134523-90-3P
134523-91-4P 134523-92-5P 134523-93-6P
134523-94-7P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)

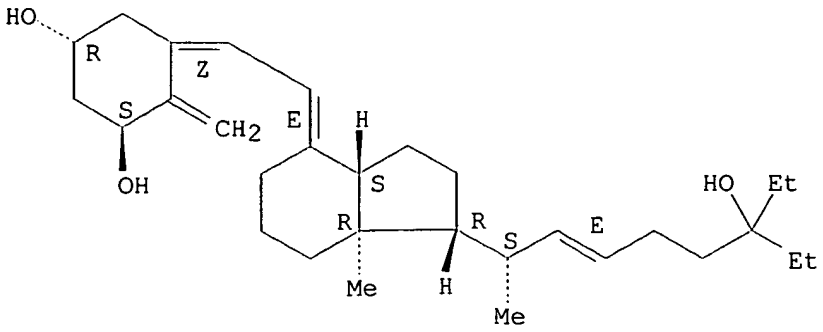
IT **1406-16-2DP**, Vitamin D, analogs
RL: PREP (Preparation)
(prepn. of, as drugs)

IT **134404-96-9P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)

RN 134404-96-9 HCAPLUS

CN 1,3-Cyclohexanediol, 5-[(2E)-[(1R,3aS,7aR)-1-[(1S,2E)-6-ethyl-6-hydroxy-1-methyl-2-octenyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

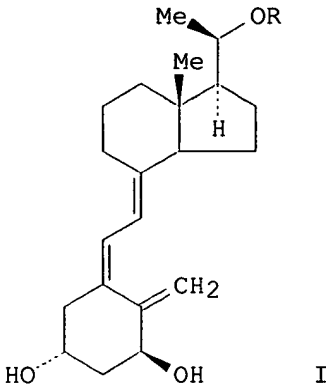
Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1991:164629 HCAPLUS
DN 114:164629
TI Preparation of vitamin D **analogs** as drugs
IN Calverley, Martin John; Hansen, Kai; Binderup, Lise
PA Leo Pharmaceutical Products Ltd. A/S, Den.
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59
CC 32-7 (Steroids)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9009991	A1	19900907	WO 1990-DK36	19900213
	W: AU, CA, FI, HU, JP, KR, NO, RO, SU, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
	CA 2044280	AA	19900824	CA 1990-2044280	19900213
	AU 9051983	A1	19900926	AU 1990-51983	19900213
	AU 627001	B2	19920813		
	EP 460032	A1	19911211	EP 1990-903793	19900213
	EP 460032	B1	19940427		
	R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	HU 59664	A2	19920629	HU 1990-2300	19900213
	HU 211025	B	19950928		
	JP 04503669	T2	19920702	JP 1990-504126	19900213
	AT 104957	E	19940515	AT 1990-903793	19900213
	ES 2055905	T3	19940901	ES 1990-903793	19900213
	RO 109939	B1	19950728	RO 1990-148060	19900213
	NO 9102902	A	19910725	NO 1991-2902	19910725
	NO 178065	B	19951009		
	NO 178065	C	19960117		
	FI 92929	B	19941014	FI 1991-3812	19910812
	FI 92929	C	19950125		
	RU 2037484	C1	19950619	RU 1991-5001741	19910822
	US 5401732	A	19950328	US 1993-16186	19930211
	LV 10428	B	19951020	LV 1993-1106	19930928
	LT 3983	B	19960625	LT 1993-1536	19931206
PRAI	GB 1989-4154	A	19890223		
	EP 1990-903793	A	19900213		
	WO 1990-DK36	A	19900213		
	US 1991-721562	B1	19910802		

OS MARPAT 114:164629
GI



I

AB The title compds. [I; R = (HO-substituted) C4-12 alkyl] and O-acyl, O-glycosyl, and phosphate ester derivs. thereof, were prepd. Thus, 1S, 3R-bis(tert-butyldimethylsilyloxy)-20S-formyl-9,10-secopregna-5E,7E,10(19)-triene was treated with air, Cu(OAc)2, 2,2'-bipyridyl, and 1,4-diazabicyclo[2-2.2]octane in DMF to give the 20-oxo deriv. This was reduced with NaBH4 in THF/MeOH to give the 20R-hydroxy compd., which was alkylated with 2-(6-bromo-2-methyl-2-hexyloxy)tetrahydro-4H-pyran. The resultant compd. was photoisomerized in CH2Cl2 contg. anthracene and Et3N using a UV lamp followed by deprotection (Bu4NF, then HF) to give I (R = CH2)4CMe2OH). I have similar or superior affinity for tumor cell receptors relative to 1,25-dihydroxy-vitamin D3, while having reduced affinity for intestinal receptors. Drug formulations contg. I [R = (CH2)3 (Et2OH] are given.

ST vitamin D analog prepn drug; antihypertensive vitamin D analog; antidiabetic vitamin D analog; antiinflammatory vitamin D analog; neoplasm inhibitor vitamin D analog; immunomodulator vitamin D analog; psoriasis treatment vitamin D analog

IT **Antidiabetics and Hypoglycemics**
Neoplasm inhibitors
(alkoxy vitamin D analogs)

IT Antihypertensives
Immunomodulators
Inflammation inhibitors
(alkoxy vitamin D derivs.)

IT Psoriasis
(treatment of, alkoxy vitamin D analogs)

IT Inflammation inhibitors
(antirheumatics, alkoxy vitamin D analogs)

IT 14660-52-7, Ethyl 5-bromopentanoate
RL: RCT (Reactant)
(Grignard reaction of, with methylmagnesium iodide)

IT 630-19-3, Pivaldehyde
RL: RCT (Reactant)
(Wittig reaction of, with isobutyrylmethylphosphonate)

IT 7751-67-9
RL: RCT (Reactant)
(Wittig reaction of, with pivaldehyde)

IT 932-86-5 35354-37-1, 1-Bromo-5-methylhexane 128312-87-8 128313-07-5 128313-15-5
RL: RCT (Reactant)
(etherification reaction of, with hydroxy vitamin D deriv.)

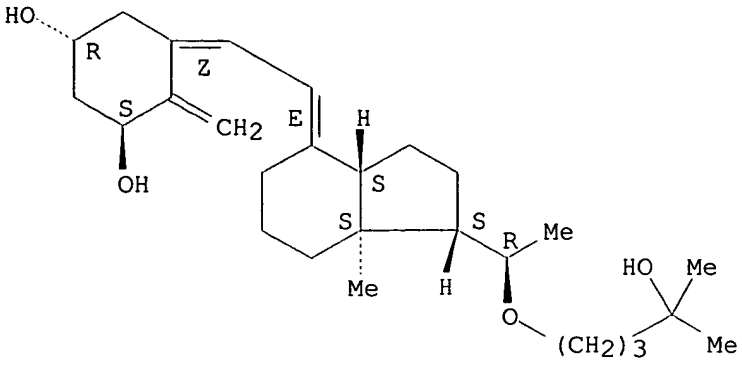
IT 870-63-3, 3,3-Dimethylallyl bromide
RL: RCT (Reactant)
(etherification reaction of, with hydroxy vitamin d deriv.)

IT 128312-85-6 128312-86-7 131875-37-1
RL: RCT (Reactant)
(etherificaton reaction of, with hydroxy vitamin D deriv.)

IT 131711-72-3P

RL: SPN (Synthetic preparation); FORM (Formation, nonpreparative); PREP (Preparation)
(formation of, prepn. of vitamin D analog)
IT 131711-78-9P, 6-Bromo-2-methyl-2-hexanol
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and conversion of, to tetrahydropyran ether deriv.)
IT 131875-36-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and conversion of, to trifluoromethanesulfonate deriv.)
IT 131711-77-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and etherification reaction of, with hydroxy-vitamin d analog)
IT 131875-35-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and ozonolysis of, in prepn. of vitamin D analog)
IT 106059-49-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and redn. of, in prepn. of vitamin d analog)
IT **131875-07-5P 131875-08-6P 131875-09-7P**
131875-10-0P 131875-11-1P 131875-12-2P
131875-13-3P 131875-14-4P 131875-15-5P
131875-16-6P 132014-43-8P 132014-44-9P
132071-85-3P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)
IT 67-97-0DP, Vitamin D3, alkoxy derivs.
RL: PREP (Preparation)
(prepn. of, as drugs)
IT 59431-24-2P 89031-83-4P 103483-32-5P 131711-71-2P 131711-77-8P
131830-01-8P 131875-05-3P **131875-06-4P 131875-17-7P**
131875-18-8P 131875-19-9P 131875-20-2P 131875-21-3P 131875-22-4P
131875-23-5P 131875-24-6P 131875-25-7P 131875-26-8P 131875-27-9P
131875-28-0P 131875-29-1P 131875-30-4P 131875-31-5P 131875-32-6P
131875-33-7P 131875-34-8P 132014-45-0P **132014-46-1P**
132014-47-2P 132014-48-3P 132014-49-4P 132014-50-7P 132014-51-8P
132014-52-9P 132014-53-0P 132014-54-1P 132014-55-2P 132015-59-9P
132015-60-2P 133005-82-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for vitamin D analog)
IT 112828-13-4
RL: RCT (Reactant)
(reaction of, in prepn. of vitamin D analog)
IT 928-51-8 2009-83-8
RL: RCT (Reactant)
(silylation of)
IT **131875-07-5P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)
RN 131875-07-5 HCAPLUS
CN 1,3-Cyclohexanediol, 4-methylene-5-[(2E)-[(1S,3aS,7aS)-octahydro-1-[(1R)-1-[(4-hydroxy-4-methylpentyl)oxy]ethyl]-7a-methyl-4H-inden-4-ylidene]ethylidene]-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 33 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1990:478822 HCAPLUS
DN 113:78822
TI Preparation of vitamin D **analogs** as drugs
IN Calverley, Martin John; Binderup, Lise; Binderup, Ernst Torndal
PA Leo Pharmaceutical Products Ltd., Den.
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C172-00
CC 32-7 (Steroids)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 8910351	A1	19891102	WO 1989-DK79	19890407
	W: AU, DK, JP, KR, US				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	AU 8935443	A1	19891124	AU 1989-35443	19890407
	AU 614372	B2	19910829		
	EP 412110	A1	19910213	EP 1989-905648	19890407
	EP 412110	B1	19930707		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	JP 03504377	T2	19910926	JP 1989-504872	19890407
	AT 91282	E	19930715	AT 1989-905648	19890407
	ZA 8902824	A	19911127	ZA 1989-2824	19890418
	DK 9002426	A	19901008	DK 1990-2426	19901008
	DK 173457	B1	20001127		
	US 5206229	A	19930427	US 1990-582944	19901010
PRAI	GB 1988-9466	A	19880421		
	GB 1988-9467	A	19880421		
	GB 1988-30169	A	19881223		
	GB 1988-30174	A	19881223		
	EP 1989-905648	A	19890407		
	WO 1989-DK79	A	19890407		

OS MARPAT 113:78822
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; n = 1-7; R1, R2 = H, alkyl; or CR1R2 may form a carbocyclic ring; R3 = R4 = H; or R3R4 = double bond], useful as immunostimulants, antidiabetics, antihypertensives, antiinflammatories (no data), etc., are prepd. Thus, a 9,10-secosteroid deriv. II was heated with Bu4NF in THF at 60.degree. and the resulting diol III was heated with

pyridinium p-toluenesulfonate in EtOH at 50.degree. to give I [R1R2 = (CH2)2, R3 = R4 = H, n = 1]. A dermatol. cream and an oral capsule contg. I as the active ingredient were formulated.

ST vitamin D analog prepn drug; immunostimulant vitamin D analog prepn; antidiabetic vitamin D analog prepn; antihypertensive ovitamin D analog prepn; antiinflammatory vitamin D analog prepn

IT Animal cell
(proliferation of, inhibitors of, vitamin D analogs as)

IT Psoriasis
(treatment of, vitamin D analogs for)

IT **Antidiabetics and Hypoglycemics**
Antihypertensives
Immunostimulants
Inflammation inhibitors
Neoplasm inhibitors
(vitamin D analogs)

IT 9,10-Secosteroids
RL: SPN (Synthetic preparation); PREP (Preparation)
(hydroxy, unsatd., prepn. of, as drugs)

IT 74-88-4, reactions 74-96-4, Ethyl bromide
RL: RCT (Reactant)
(Grignard reaction of, with bromopentanoate deriv.)

IT **114694-09-6P 120336-95-0P 123963-51-9P**
123963-52-0P 125448-38-6P 128312-71-0P
128312-72-1P 128312-73-2P 128312-74-3P
128312-75-4P 128312-76-5P 128312-77-6P
128357-75-5P 128357-85-7P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)

IT 19525-80-5P 40894-17-5P 74723-52-7P 114694-18-7P 117201-93-1P
123963-59-7P 128312-70-9P 128312-78-7P 128312-79-8P 128312-80-1P
128312-81-2P 128312-82-3P 128312-83-4P 128312-84-5P 128312-85-6P
128312-86-7P 128312-87-8P 128312-88-9P 128312-89-0P 128312-90-3P
128312-91-4P 128312-92-5P 128312-93-6P 128312-94-7P 128312-95-8P
128312-96-9P 128312-97-0P 128312-98-1P 128312-99-2P 128313-00-8P
128313-01-9P 128313-02-0P 128313-03-1P 128313-04-2P 128313-05-3P
128313-06-4P 128313-07-5P 128313-08-6P 128313-09-7P 128313-10-0P
128313-11-1P 128313-12-2P 128313-13-3P 128313-14-4P 128313-15-5P
128313-16-6P 128313-17-7P 128332-74-1P 128332-75-2P 128387-25-7P
128387-26-8P 128387-27-9P 128387-28-0P 128387-29-1P 128387-30-4P
128387-31-5P 128387-32-6P 128387-33-7P 128387-34-8P 128387-35-9P
128387-36-0P 128387-37-1P 128387-38-2P 128440-09-5P 128440-75-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for vitamin D analogs)

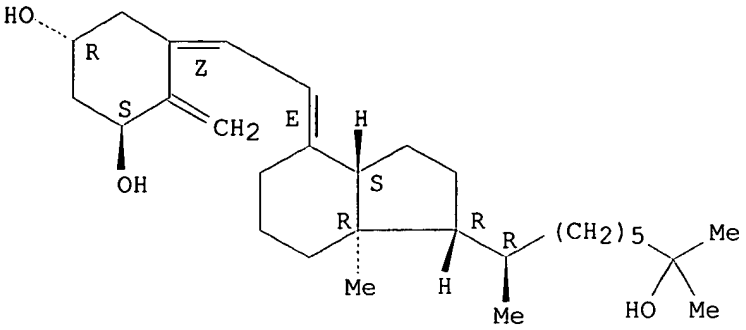
IT 75-77-4, Trimethylsilyl chloride, reactions 98-59-9, p-Toluenesulfonyl chloride 110-87-2 590-90-9, 4-Hydroxy-2-butanone 829-85-6, Diphenylphosphine 5326-50-1 13195-66-9 14660-52-7, Ethyl 5-bromopentanoate 25542-62-5, Ethyl 6-bromohexanoate 40894-06-2 59780-24-4 112670-81-2
RL: RCT (Reactant)
(reaction of, in prepn. of vitamin D analogs)

IT **114694-09-6P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)

RN 114694-09-6 HCAPLUS

CN 1,3-Cyclohexanediol, 4-methylene-5-[(2E)-[(1R,3aS,7aR)-octahydro-1-[(1R)-7-hydroxy-1,7-dimethyloctyl]-7a-methyl-4H-inden-4-ylidene]ethylidene]-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

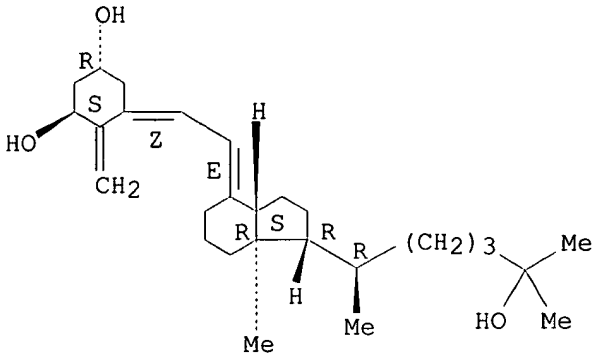
Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 34 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1987:490864 HCAPLUS
DN 107:90864
TI 1,25-Dihydroxyvitamin D3 target cells in immature pancreatic islets
AU Clark, Samuel A.; Stumpf, Walter E.; Sar, Madhabananda; **DeLuca, Hector F.**
CS Dep. Anat., Univ. North Carolina, Chapel Hill, NC, 27514, USA
SO Am. J. Physiol. (1987), 253,(1, Pt. 1), E99-E105
CODEN: AJPHAP; ISSN: 0002-9513
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Target cells of 1,25-dihydroxyvitamin D3 (I) were identified by autoradiog. in islets from rats of different ages. Nuclei of pancreatic islet cells selectively concd. [3H]I but not 25-[3H]hydroxyvitamin D3 or 24,25-[3H]dihydroxyvitamin D3. Developmental studies of pancreatic islets indicated that target cells, as revealed by significant nuclear concn. of [3H]I, are present in islet cells of fetal rats. The percentage of islet cells that concd. [3H]I increased from 10 to 15% in the fetus to 60% at 1 day of age. Immunocytochem. staining indicated that insulin-contg. cells, but not glucagon or somatostatin cells, concd. [3H]I. Peak uptake of [3H]I was calcd. to be 400 pmol/mg DNA, with no significant difference in nuclear accumulation between islet cells from neonatal and adult rats or between islets in vivo and isolated islets in vitro. Apparently, I target cells are present in islets before pancreatic .beta.-cells are morphol. or functionally mature and islet .beta.-cells conc. I, but not 25-hydroxyvitamin D3 or 24,25-dihydroxyvitamin D3. It is concluded that only the 1,25-dihydroxyvitamin D3 metabolite of vitamin D is accumulated by nuclei of developing and mature .beta.-cells and 1,25-dihydroxyvitamin D3 plays a role in the maturation of islet .beta.-cells.
ST dihydroxyvitamin D3 pancreas fetus newborn; receptor dihydroxycholecalciferol pancreas ontogeny
IT Intestine, metabolism
Kidney, metabolism
Parathyroid gland
(dihydroxyvitamin D3 uptake by)
IT Newborn
(dihydroxyvitamin D3 uptake by pancreatic islets of)
IT Osteoblast
(dihydroxyvitamin D3 uptake by, of fetus, pancreatic islet in relation to)
IT Cell nucleus
(dihydroxyvitamin D3 uptake by, of pancreatic islet of fetus and newborn)
IT Receptors
RL: BIOL (Biological study)
(for dihydroxyvitamin D3, of pancreatic islet of fetus and newborn)
IT Biological transport
(absorption, of dihydroxyvitamin D3, by pancreatic islet of fetus and newborn)

IT Embryo
(fetus, dihydroxyvitamin D3 uptake by pancreatic islets of)
IT **Pancreatic islet of Langerhans**
(.beta.-cell, dihydroxyvitamin D3 uptake by, of fetus and newborn)
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: PROC (Process)
(uptake of, by pancreatic islet of fetus and newborn)
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: PROC (Process)
(uptake of, by pancreatic islet of fetus and newborn)
RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 35 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1986:514055 HCAPLUS
DN 105:114055
TI Islet insulin release and net calcium retention in vitro in vitamin D-deficient rats
AU Chertow, Bruce S.; Sivitz, W. I.; Baranetsky, N. G.; Cordle, M. B.; **DeLuca, H. F.**
CS Sch. Med., Marshall Univ., Huntington, WV, 25701, USA
SO Diabetes (1986), 35(7), 771-5
CODEN: DIAEAZ; ISSN: 0012-1797
DT Journal
LA English
CC 18-2 (Animal Nutrition)
AB Perfused islets from vitamin D [**1406-16-2**]-deficient (D-def) rats showed marked impairment of glucose-induced biphasic release, accounted for at least in part by a decrease in food intake. D-def rat islets were examd. for an impaired response to 5.6 mM glucose or tolbutamide (T) [64-77-7], and whether this impairment is related to a decrease in food intake or a defect in islet Ca metab. Compared with secretion from normal islets, biphasic insulin [**9004-10-8**] release from islets of both D-def rats and pair-fed (PF) rats was diminished by >50% in response to 5.6 mM glucose alone or 5.6 mM glucose plus T. Insulin secretion was not significantly different between islets of D-def rats and islets of PF rats. In contrast, net Ca retention in islets of D-def rats was decreased to 68% of retention in islets of PF rats. However, net Ca retention in islets of both PF and D-def rats increased in response to T. The pair-feeding expts. suggest that the decrease in insulin release from islets of D-def rats is due to the decrease in food intake assocd. with the D-def state. On the other hand, the defect in Ca retention in islets of D-def rats raises the possibility that vitamin D may have a specific effect on islet Ca metab. In this case, the mechanism of impaired insulin release in islets of D-def rats would be different from that in islets of PF rats and would involve a

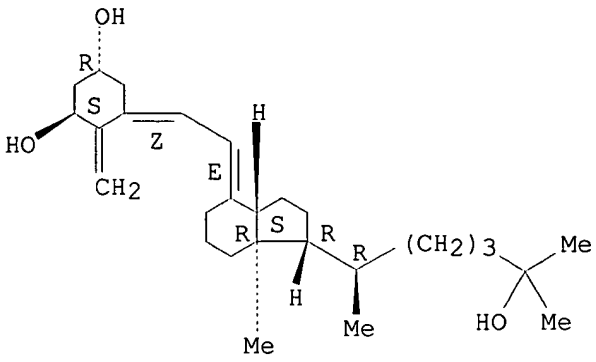
defect in intracellular Ca handling.
ST vitamin D deficiency islet insulin calcium
IT **Pancreatic islet of Langerhans**
(insulin release and calcium retention by, in vitamin D deficiency)
IT **1406-16-2**
RL: BIOL (Biological study)
(deficiency of, insulin release and calcium retention by islets response to)
IT 64-77-7
RL: BIOL (Biological study)
(in study of insulin release by islets in vitamin D deficiency)
IT **9004-10-8**, biological studies
RL: BIOL (Biological study)
(release of, by pancreatic islets in vitamin D deficiency, calcium retention in relation to)
IT 7440-70-2, biological studies
RL: BIOL (Biological study)
(retention of, by pancreatic islets in vitamin D deficiency, insulin release in relation to)
IT **1406-16-2**
RL: BIOL (Biological study)
(deficiency of, insulin release and calcium retention by islets response to)
RN 1406-16-2 HCAPLUS
CN Vitamin D (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L81 ANSWER 36 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1985:40622 HCAPLUS
DN 102:40622
TI Activation and fusion induced by 1.alpha.,25-dihydroxyvitamin D3 and their relation in alveolar macrophages
AU Abe, Etsuko; Shiina, Yoshiko; Miyaura, Chisato; Tanaka, Hirofumi; Hayashi, Takamune; Kanegasaki, Shiro; Saito, Motoo; Nishii, Yasuho; **DeLuca, Hector F.**; Suda, Tatsuo
CS Sch. Dent., Showa Univ., Tokyo, 142, Japan
SO Proc. Natl. Acad. Sci. U. S. A. (1984), 81(22), 7112-16
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
CC 2-9 (Mammalian Hormones)
AB 1.alpha.,25-Dihydroxyvitamin D3 [1.alpha.,25-(OH)2D3] [**32222-06-3**] induced fusion of murine alveolar macrophages. This effect was obsd. in growth medium contg. 5% human serum but not in the medium with 5% fetal bovine serum. Unlike 1.alpha.,25-(OH)2D3, bacterial lipopolysaccharides (LPS) did not induce fusion of alveolar macrophages. However, both 1.alpha.,25-(OH)2D3 and LPS activated alveolar macrophages, as measured by glucose [**50-99-7**] consumption, increase in Fc receptors, and induction of cytotoxicity. The no. of Fc receptors on the surface of multinucleated giant cells induced by 1.alpha.,25-(OH)2D3 was much smaller than that on the surface of mononuclear macrophages treated with the hormone. Thus, 1.alpha.,25-(OH)2D3 induced both fusion and activation of alveolar macrophages, whereas LPS elicited activation only.
ST dihydroxyvitamin D3 activation fusion alveolar macrophage; lipopolysaccharide alveolar macrophage activation
IT Lipopolysaccharides
RL: BIOL (Biological study)
(alveolar macrophage activation by)
IT Macrophage
(alveolar, activation and fusion in, dihydroxyvitamin D3 effect on)
IT Receptors
RL: BIOL (Biological study)
(for Fc antigen, of alveolar macrophages, dihydroxyvitamin D3 and lipopolysaccharide effect on)
IT Toxicity

(cyto-, of alveolar macrophages, dihydroxyvitamin D3 and lipopolysaccharides effect on)
IT **32222-06-3**
RL: BIOL (Biological study)
(alveolar macrophage activation and fusion induction by)
IT **50-99-7**, biological studies
RL: BIOL (Biological study)
(consumption of, by alveolar macrophages, dihydroxyvitamin D3 and lipopolysaccharide effect on)
IT **32222-06-3**
RL: BIOL (Biological study)
(alveolar macrophage activation and fusion induction by)
RN 32222-06-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)

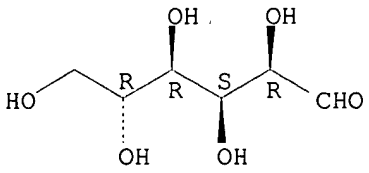
Absolute stereochemistry.
Double bond geometry as shown.



L81 ANSWER 37 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1984:453762 HCAPLUS
DN 101:53762
TI Complex carbohydrate diets are not capable of maintaining normal plasma calcium and phosphorus levels in vitamin D-deficient rats
AU Underwood, Johnnie L.; Phelps, Mary E.; **DeLuca, Hector F.**
CS Coll. Agric. Life Sci., Univ. Wisconsin, Madison, WI, 53706, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1984), 81(8), 2352-3
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
CC 18-2 (Animal Nutrition)
AB Substitution of cerelose (glucose monohydrate) [**50-99-7**] with complex carbohydrate (whole wheat flour) did not alter plasma Ca levels in vitamin D [**1406-16-2**]-deficient rats, contrary to a previous report. It is suspected that whole wheat flour may contain traces of vitamin D that result in a slower rate of depletion than found with cerelose diets. Vitamin D-deficient rats showing low plasma 1,25-dihydroxyvitamin D3 levels and no detectable 25-hydroxyvitamin D3 levels in their blood showed hypocalcemia (5.6 mg/dL) and normal phosphatemia, whether fed whole wheat or cerelose diets.
ST carbohydrate diet plasma mineral vitamin D; cerelose diet plasma mineral vitamin D; flour diet plasma mineral vitamin D; plasma mineral diet carbohydrate vitamin D; calcium plasma diet carbohydrate vitamin D; phosphorus plasma diet carbohydrate vitamin D
IT Carbohydrates and Sugars, biological studies
RL: BIOL (Biological study)
(calcium and phosphorus of blood plasma in relation to dietary type of, in vitamin D deficiency)
IT Blood plasma
(calcium and phosphorus of, in vitamin D deficiency, dietary cerelose

and wheat flour effect on)
IT Wheat flour
(calcium and phosphrous of blood plasma response to dietary, in vitamin D deficiency)
IT **50-99-7**, biological studies
RL: BIOL (Biological study)
(calcium and phosphrous of **blood** plasma response to dietary, in vitamin D deficiency)
IT **1406-16-2**
RL: BIOL (Biological study)
(deficiency of, calcium and phosphorus of blood plasma in, dietary cerelose and wheat flour effect on)
IT 7440-70-2, biological studies 7723-14-0, biological studies
RL: BIOL (Biological study)
(of blood plasma, in vitamin D deficiency, dietary cerelose and wheat flour effect on)
IT **50-99-7**, biological studies
RL: BIOL (Biological study)
(calcium and phosphrous of **blood** plasma response to dietary, in vitamin D deficiency)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L81 ANSWER 38 OF 39 HCAPLUS COPYRIGHT 2001 ACS
AN 1983:574631 HCAPLUS
DN 99:174631
TI Cellular mechanisms of insulin release: the effects of vitamin D deficiency and repletion on rat insulin secretion
AU Chertow, Bruce S.; Sivitz, William I.; Baranetsky, Nicholas G.; Clark, Samuel A.; Waite, Alan; **Deluca, Hector F.**
CS Sch. Med., Marshall Univ., Huntington, WV, 25701, USA
SO Endocrinology (Baltimore) (1983), 113(4), 1511-18
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
CC 18-2 (Animal Nutrition)
Section cross-reference(s): 2
AB To det. whether impaired insulin [**9004-10-8**] release from perifused rat islets of vitamin D [**1406-16-2**]-deficient (D-def) rats is a result of vitamin D deficiency specifically or an assocd. decrease in food intake, insulin release from islets of vitamin D-def rats was compared with insulin release from islets of pair fed (pf) normal rats, and the effects of 1,25-dihydroxyvitamin D3 (I) [**32222-06-3**] treatment on food intake and insulin secretion from islets of D-def rats were measured. Both vitamin D-def and pf normal rat islets showed significantly diminished insulin release in comparison with normal controls but were not different from each other. When D-def rats were repleted with I, food intake increased and insulin secretion improved during perifusion of rat islets. When D-def rats treated with I were prevented from increasing their food intake in response to I by pair feeding to a group of untreated D-def rats, insulin release from islets of treated rats was not significantly different from untreated D-def rats. To sep. the effects of vitamin D deficiency from hypocalcemia, a group of vitamin D-def hypocalcemic rats was compared with a group of D-def normocalcemic rats. Normocalcemia did not reverse the defect in insulin

release. In studies of cellular Ca uptake, both pf and D-def rat islets took up less Ca than normal islets but Ca uptake was not different between pf and D-def rat islets. The studies suggest that vitamin D deficiency is assocd. with marked impairment of biphasic insulin release and that the decrease in food intake may account for this impairment at least in part.

ST vitamin D insulin secretion

IT **Pancreatic islet of Langerhans**
(insulin secretion by, vitamin D deficiency and repletion effect on)

IT **1406-16-2**
RL: BIOL (Biological study)
(deficiency of, insulin secretion in, repletion effect on)

IT **32222-06-3**
RL: BIOL (Biological study)
(insulin secretion in response to, in vitamin D deficiency)

IT **9004-10-8**, biological studies
RL: BIOL (Biological study)
(secretion of, in vitamin D deficiency and repletion)

IT **1406-16-2**
RL: BIOL (Biological study)
(deficiency of, insulin secretion in, repletion effect on)

RN 1406-16-2 HCAPLUS

CN Vitamin D (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L81 ANSWER 39 OF 39 HCAPLUS COPYRIGHT 2001 ACS

AN 1980:579944 HCAPLUS

DN 93:179944

TI Target cells for 1,25 dihydroxyvitamin D3 in the pancreas

AU Clark, Samuel A.; Stumpf, Walter E.; Sar, Madhabananda; **DeLuca, Hector F.**; Tanaka, Yoko

CS Dep. Anat., Univ. North Carolina, Chapel Hill, NC, 27514, USA

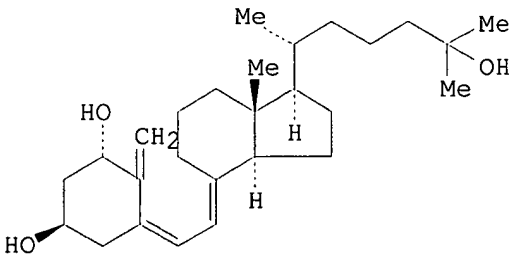
SO Cell Tissue Res. (1980), 209(3), 515-20
CODEN: CTSRCS; ISSN: 0302-766X

DT Journal

LA English

CC 2-1 (Hormone Pharmacology)

GI



I

AB Mature rats raised on a vitamin D-deficient diet were injected with 3H-labeled 1,25 dihydroxyvitamin D3 (I) [**32511-63-0**]. Concn. of radioactivity, which is prevented by pretreatment with unlabeled I, is found in nuclei of cells that are centrally located in pancreatic islets. The central location of these cells and supportive evidence from the literature suggest that they are .beta.-cells, and that I has a direct and genomic action on .beta.-cell functions including insulin secretion.

ST pancreatic islet dihydroxyvitamin D3; vitamin D3 dihydroxy pancreas; cholecalciferol dihydroxy pancreas; hydroxyvitamin D3 pancreatic islet

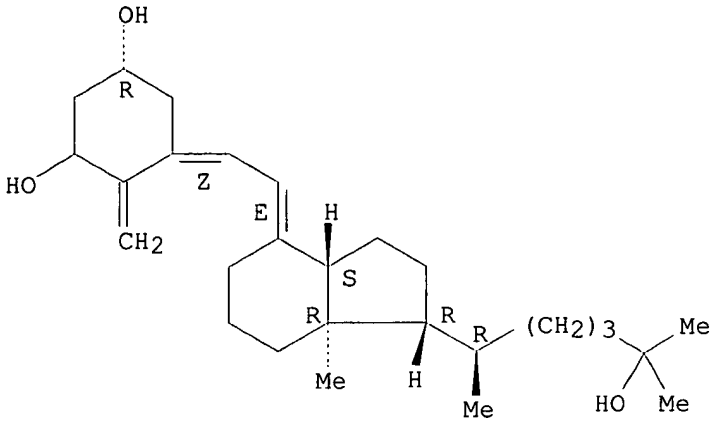
IT **Pancreatic islet of Langerhans**
(dihydroxyvitamin D3 uptake by)

IT Cell nucleus
(dihydroxyvitamin D3 uptake by, of pancreatic islet)

IT **32511-63-0**

RL: BIOL (Biological study)
(pancreatic islet target cells for)
IT **32511-63-0**
RL: BIOL (Biological study)
(pancreatic islet target cells for)
RN 32511-63-0 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (3.beta.,5Z,7E)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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DICTIONARY FILE UPDATES: 14 SEP 2001 HIGHEST RN 357154-15-5

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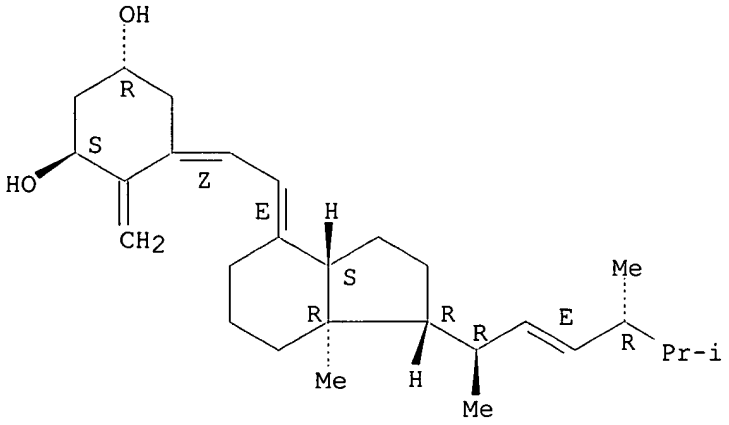
L94 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN **54573-75-0** REGISTRY
CN 9,10-Secoergosta-5,7,10(19),22-tetraene-1,3-diol,
(1.alpha.,3.beta.,5Z,7E,22E)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Hydroxyergocalciferol
CN 1-Hydroxyvitamin D2
CN 1.alpha.-Hydroxyergocalciferol
CN 1.alpha.-Hydroxyvitamin D2
CN Doxercalciferol
CN Hectorol
CN TSA 840
FS STEREOSEARCH
DR 125285-48-5, 87649-67-0
MF C28 H44 O2
LC STN Files: ADISINSIGHT, ADISNEWS, BEILSTEIN*, BIOSIS, BIOTECHNO, CA,

CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



97 REFERENCES IN FILE CA (1967 TO DATE)
97 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:175935

REFERENCE 2: 135:56096

REFERENCE 3: 134:362292

REFERENCE 4: 134:336139

REFERENCE 5: 134:172896

REFERENCE 6: 134:105886

REFERENCE 7: 134:42317

REFERENCE 8: 134:42316

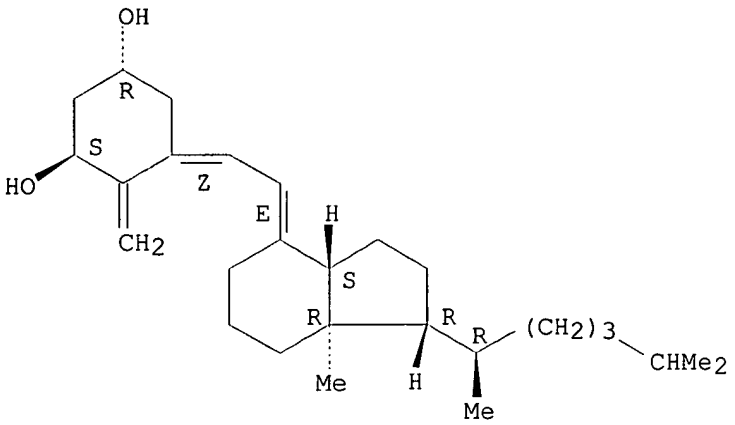
REFERENCE 9: 134:42315

REFERENCE 10: 134:42314

L94 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN **41294-56-8** REGISTRY
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3-diol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN .alpha.-Calcidol
CN 1-Hydroxycholecalciferol
CN 1-Hydroxyvitamin D3
CN 1.alpha.-Hydroxycholecalciferol
CN 1.alpha.-Hydroxyvitamin D3
CN Alfacalcidol
CN Alfarol
CN Alphacalcidol
CN Oxydevit
CN Un Alpha
FS STEREOSEARCH

DR 125324-15-4, 41461-06-7, 43157-29-5, 43217-90-9
MF C27 H44 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, IPA, MEDLINE, MRCK*, NAPRALERT, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



1034 REFERENCES IN FILE CA (1967 TO DATE)
23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1034 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:175935

REFERENCE 2: 135:116249

REFERENCE 3: 135:56413

REFERENCE 4: 135:41381

REFERENCE 5: 135:368

REFERENCE 6: 134:361111

REFERENCE 7: 134:339134

REFERENCE 8: 134:336139

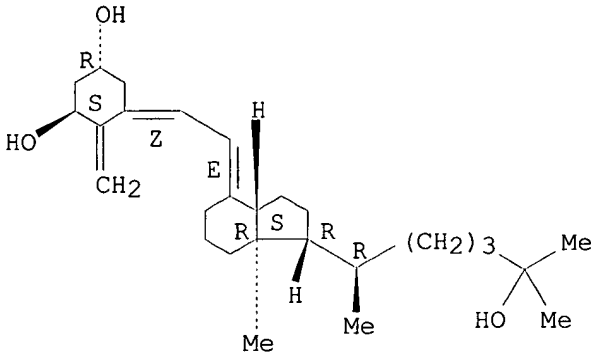
REFERENCE 9: 134:275468

REFERENCE 10: 134:251647

L94 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN **32222-06-3** REGISTRY
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,25-Dihydroxycholecalciferol
CN 1,25-Dihydroxyvitamin D
CN 1,25-Dihydroxyvitamin D3
CN 1.alpha.,25-(OH)2D3

CN 1.alpha.,25-Dihydroxycholecalciferol
CN 1.alpha.,25-Dihydroxyvitamin D3
CN Calcijex
CN Calcitriol
CN Ro 21-5535
CN Rocaltrol
CN Silkis
CN Soltriol
CN Topitriol
FS STEREOSEARCH
DR 125338-24-1
MF C27 H44 O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.
Double bond geometry as shown.



8634 REFERENCES IN FILE CA (1967 TO DATE)
241 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8641 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:179665

REFERENCE 2: 135:179633

REFERENCE 3: 135:176020

REFERENCE 4: 135:175977

REFERENCE 5: 135:175960

REFERENCE 6: 135:175948

REFERENCE 7: 135:175933

REFERENCE 8: 135:175628

REFERENCE 9: 135:175540

REFERENCE 10: 135:175539

L94 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2001 ACS

RN **1406-16-2** REGISTRY
CN Vitamin D (8CI, 9CI) (CA INDEX NAME)
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMLIST, CIN, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
6048 REFERENCES IN FILE CA (1967 TO DATE)
682 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6053 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:180067

REFERENCE 2: 135:178753

REFERENCE 3: 135:177398

REFERENCE 4: 135:175661

REFERENCE 5: 135:175540

REFERENCE 6: 135:175486

REFERENCE 7: 135:175468

REFERENCE 8: 135:174733

REFERENCE 9: 135:166318

REFERENCE 10: 135:162482

=> fil medline
FILE 'MEDLINE' ENTERED AT 13:56:48 ON 16 SEP 2001

FILE LAST UPDATED: 13 SEP 2001 (20010913/UP). FILE COVERS 1958 TO DATE.

On April 22, 2001, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE now contains IN-PROCESS records. See HELP CONTENT for details.

MEDLINE is now updated 4 times per week. A new current-awareness alert frequency (EVERYUPDATE) is available. See HELP UPDATE for more information.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2001 vocabulary. Enter HELP THESAURUS for details.

The OLDMEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> d all tot

L115 ANSWER 1 OF 14 MEDLINE
AN 2001252985 MEDLINE
DN **21250782** PubMed ID: **11352495**
TI 1alpha, 25-Dihydroxyvitamin D3 suppresses the effect of streptozotocin-induced diabetes during chemical rat liver carcinogenesis.
AU Saha B K; Sarkar A; Basak R; Chatterjee M
CS Division of Biochemistry, Department of Pharmaceutical Technology, Jadavpur University, Calcutta, 700 032, India.
SO CELL BIOLOGY INTERNATIONAL, (2001) 25 (3) 227-37.
Journal code: BPN; 9307129. ISSN: 1065-6995.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200107
ED Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705
AB The effect of streptozotocin-induced diabetes in male Sprague-Dawley rats was investigated to ascertain whether it has had any modulating role in hepatocarcinogenesis. Hepatocarcinogenesis was initiated with a single sub-necrogenic dose of diethylnitrosamine (DEN) (125 mg/kg body weight, i.p.) whilst acute diabetes was produced with a single i.p. injection of streptozotocin (STZ) (65 mg/kg body weight). STZ was administered either before or after initiation with DEN at 3-week intervals. With this basic experimental regimen, the effect of an antioxidant vitamin, 1alpha, 25-dihydroxyvitamin D3 (VD) (0.3 microg/ 0.1 ml propylene glycol per os twice a week), was investigated with effect from 4 weeks prior to the exposure of DEN or STZ. Primary routine histopathology, hepatic nodular morphometric analysis and major preneoplastic antioxidant and drug metabolising enzymes were tested either with or without VD treatment in different experimental and control groups. Observation of the hepatic nodulogenesis, pathology and level of the antioxidant and drug metabolising enzyme pattern of the tissue showed a marked protection in different experimental groups of rats treated with VD. It may be that VD could elicit an anticarcinogenic potential in the aforesaid regimen by resetting the effects of these biomarkers induced by DEN and/or STZ. We further propose that STZ, when administered 3 weeks after DEN, caused massive damage where its action in vivo could be comparable with any known promoter that could propel the process of carcinogenesis more efficiently than when it was applied before the carcinogen. Copyright 2001 Academic Press.
CT Check Tags: Animal; Male
Alkylating Agents: PD, pharmacology
*Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
Antioxidants: PD, pharmacology
Antioxidants: TU, therapeutic use
Blood Glucose: AN, analysis
Cytochrome P-450: ME, metabolism
Cytosol: DE, drug effects
Cytosol: ME, metabolism
***Diabetes Mellitus, Experimental: CI, chemically induced**
*Diethylnitrosamine: PD, pharmacology
Glutathione: ME, metabolism
Glutathione Transferase: ME, metabolism
Lipid Peroxidation: DE, drug effects
*Liver Neoplasms: CI, chemically induced
Liver Neoplasms: DT, drug therapy
Liver Neoplasms: ME, metabolism
*Liver Neoplasms: PA, pathology
Microsomes, Liver: DE, drug effects
Microsomes, Liver: EN, enzymology
Rats
Rats, Sprague-Dawley
*Streptozocin: AI, antagonists & inhibitors

Streptozocin: PD, pharmacology
Vitamin D: AA, analogs & derivatives
***Vitamin D: PD, pharmacology**
Vitamin D: TU, therapeutic use
gamma-Glutamyltransferase: ME, metabolism
RN **1406-16-2 (Vitamin D)**; 18883-66-4 (Streptozocin); 55-18-5 (Diethylnitrosamine); 70-18-8 (Glutathione); 9035-51-2 (Cytochrome P-450)
CN 0 (2-methyl-1,25-dihydroxyvitamin D3); 0 (Alkylating Agents); 0 (Antineoplastic Agents); 0 (Antioxidants); 0 (Blood **Glucose**); EC 2.3.2.2 (gamma-Glutamyltransferase); EC 2.5.1.18 (Glutathione Transferase)

L115 ANSWER 2 OF 14 MEDLINE
AN 1999149824 MEDLINE
DN **99149824** PubMed ID: **10027578**
TI Vitamin D supplement in early childhood and risk for Type I (**insulin**-dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group.
AU Anonymous
SO DIABETOLOGIA, (1999 Jan) 42 (1) 51-4.
Journal code: E93; 0006777. ISSN: 0012-186X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LA English
FS Priority Journals
EM 199904
ED Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990426
AB The initiation of the immunopathogenetic process that can lead to Type I (**insulin**-dependent) diabetes mellitus in childhood probably occurs early in life. Studies in vitro have shown that vitamin D3 is immunosuppressive or immunomodulating and studies in experimental models of autoimmunity, including one for autoimmune diabetes, have shown vitamin D to be protective. Seven centres in Europe with access to population-based and validated case registers of **insulin** -dependent diabetes patients participated in a case-control study focusing on early exposures and risk of Type I diabetes. Altogether data from 820 patients and 2335 control subjects corresponding to 85% of eligible patients and 76% of eligible control subjects were analysed. Questions focused on perinatal events and early eating habits including vitamin D supplementation. The frequency of vitamin D supplementation in different countries varied from 47 to 97% among control subjects. Vitamin D supplementation was associated with a decreased risk of Type I diabetes without indication of heterogeneity. The Mantel-Haenszel combined odds ratio was 0.67 (95% confidence limits: 0.53, 0.86). Adjustment for the possible confounders: a low birth weight, a short duration of breast feeding, old maternal age and study centre in logistic regression analysis did not affect the significant protective effect of vitamin D. In conclusion, this large multicentre trial covering many different European settings consistently showed a protective effect of vitamin D supplementation in infancy. The findings indicate that activated vitamin D might contribute to immune modulation and thereby protect or arrest an ongoing immune process initiated in susceptible people by early environmental exposures.
CT Check Tags: Comparative Study; Human; Support, Non-U.S. Gov't
Adolescence
Age Factors
Age of Onset
Case-Control Studies
Child
Child, Preschool
Confidence Intervals
***Diabetes Mellitus, Insulin-Dependent: EP, epidemiology**
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
*Dietary Supplements

Europe: EP, epidemiology
Infant
Odds Ratio
Registries
Reproducibility of Results
Risk Factors
***Vitamin D: AD, administration & dosage**
Vitamin D: TU, therapeutic use
RN **1406-16-2 (Vitamin D)**

L115 ANSWER 3 OF 14 MEDLINE
AN 1998311513 MEDLINE
DN **98311513** PubMed ID: **9649179**
TI 1,25-Dihydroxyvitamin D3 restores sensitivity to cyclophosphamide-induced apoptosis in non-obese diabetic (NOD) mice and protects against diabetes.
AU Casteels K; Waer M; Bouillon R; Depovere J; Valckx D; Laureys J; Mathieu C
CS Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Katholieke Universiteit Leuven, Belgium.
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1998 May) 112 (2) 181-7.
Journal code: DD7; 0057202. ISSN: 0009-9104.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199807
ED Entered STN: 19980731
Last Updated on STN: 19990129
Entered Medline: 19980720
AB The activated form of vitamin D, 1,25(OH)2D3, and its analogues can prevent type I diabetes in NOD mice. Protection is achieved without signs of systemic immunosuppression and is associated with a restoration of the defective immune regulator system of the NOD mice. The aim of the present study was to investigate whether this restoration of regulator cell function is the only mechanism in the prevention of diabetes by 1,25(OH)2D3. We tested therefore if 1,25(OH)2D3 could prevent cyclophosphamide-induced diabetes, since diabetes occurring after cyclophosphamide injection is believed to be due to an elimination of suppresser cells. NOD mice treated with 1,25(OH)2D3 (5 microg/kg every 2 days) from the time of weaning were clearly protected against diabetes induced by cyclophosphamide (200 mg/kg body wt at 70 days old) (2/12 (17%) versus 36/53 (68%) in control mice, $P < 0.005$). By co-transfer experiments it was demonstrated that cyclophosphamide had indeed eliminated the suppresser cells present in 1,25(OH)2D3-treated mice. Since cyclophosphamide injection did not break the protection offered by 1,25(OH)2D3, it was clear that diabetogenic effector cells were affected by 1,25(OH)2D3 treatment as well. This was confirmed by the finding that splenocytes from 1,25(OH)2D3-treated mice were less capable of transferring diabetes in young, irradiated NOD mice, and by the demonstration of lower Th1 cytokine levels in the pancreases of 1,25(OH)2D3-treated, cyclophosphamide-injected mice. This better elimination of effector cells in 1,25(OH)2D3-treated mice could be explained by a restoration of the sensitivity to cyclophosphamide-induced apoptosis in both thymocytes and splenocytes, in normally apoptosis-resistant NOD mice. Altogether, these data indicate that the protection against diabetes offered by 1,25(OH)2D3 may be independent of the presence of suppresser cells, and may involve increased apoptosis of Th1 autoimmune effector cells.
CT Check Tags: Animal; Support, Non-U.S. Gov't
*Apoptosis: DE, drug effects
***Calcitriol: PD, pharmacology**
*Cyclophosphamide: PD, pharmacology
Cytokines: BI, biosynthesis
Cytokines: GE, genetics
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
*Immunosuppressive Agents: PD, pharmacology
Lymphocytes: DE, drug effects

Lymphocytes: PH, physiology
Mice
Mice, Inbred NOD
RNA, Messenger: ME, metabolism
RN **32222-06-3 (Calcitriol)**; 50-18-0 (Cyclophosphamide)
CN 0 (Cytokines); 0 (Immunosuppressive Agents); 0 (RNA, Messenger)

L115 ANSWER 4 OF 14 MEDLINE
AN 1998264311 MEDLINE
DN **98264311** PubMed ID: **9603172**
TI Prevention of autoimmune destruction of syngeneic islet grafts in spontaneously diabetic nonobese diabetic mice by a combination of a vitamin D3 analog and cyclosporine.
AU Casteels K; Waer M; Laureys J; Valckx D; Depovere J; Bouillon R; Mathieu C
CS Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Gasthuisberg, Leuven, Belgium.
SO TRANSPLANTATION, (1998 May 15) 65 (9) 1225-32.
Journal code: WEJ; 0132144. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980708
Last Updated on STN: 19980708
Entered Medline: 19980619
AB BACKGROUND: Type 1 diabetes is characterized by the presence of an autoimmune memory, responsible for the destruction of even syngeneic islet grafts. This recurrence of autoimmunity is partly responsible for the need of extensive immunosuppression in pancreas and islet transplantation in type 1 diabetic patients. The aim of the study was to evaluate the capacity of a 20-epi-analog of vitamin D3, KH1060, both alone and in combination with cyclosporine (CsA) to prevent diabetes recurrence in syngeneic islet grafts in nonobese diabetic (NOD) mice. METHODS: Spontaneously diabetic NOD mice grafted with syngeneic islets (n=500) under the kidney capsule were treated with KH1060, CsA, or a combination of both drugs from the day before transplantation until recurrence or 60 days after transplantation. RESULTS: Vehicle-treated mice showed a recurrence of diabetes in 100% of cases (n=17) within 4 weeks. Treatment with high doses of CsA (15 mg/kg/day) or KH1060 (1 microg/kg/2 days) significantly prolonged islet survival (60 days and 50 days, respectively, versus 9.5 days in controls; P<0.001 and P<0.0001). Mice treated with subtherapeutical doses of both drugs combined (KH1060 0.5 microg/kg/2 days + CsA 7.5 mg/kg/day) had significant prolongation of graft survival (48 days; P<0.001) and more importantly, four of five mice that were still normoglycemic 60 days after transplantation showed no recurrence after discontinuation of all treatment. Histology of the grafts of control and combination-treated mice demonstrated that graft infiltration and islet destruction were less severe in grafts of combination-treated mice. Cytokine mRNA analysis in the grafts 6 days after transplantation revealed a clear suppression of interleukin-12 and T helper 1 cytokines and higher levels of interleukin-4 in combination-treated mice. CONCLUSIONS: KH1060, an analog of 1,25(OH)2D3, delays autoimmune disease recurrence after syngeneic islet transplantation in NOD mice, both alone and especially in combination with CsA, possibly restoring tolerance to beta cells in 30% of cases.
CT Check Tags: Animal; Support, Non-U.S. Gov't
*Autoimmunity: PH, physiology
Calcitriol: AA, analogs & derivatives
Calcitriol: PD, pharmacology
Calcium: ME, metabolism
***Cholecalciferol: AA, analogs & derivatives**
Cyclosporine: AE, adverse effects
Cyclosporine: PD, pharmacology
***Diabetes Mellitus: GE, genetics**
Diabetes Mellitus: IM, immunology

***Diabetes Mellitus: SU, surgery**
Drug Combinations
Immunosuppressive Agents: AE, adverse effects
Immunosuppressive Agents: PD, pharmacology
Insulin: AN, analysis
Islets of Langerhans: CH, chemistry
Islets of Langerhans: PA, pathology
*Islets of Langerhans Transplantation
Mice
Mice, Inbred NOD
Recurrence: PC, prevention & control
Transplantation, Isogeneic
RN **11061-68-0 (Insulin)**; **131875-08-6 (KH 1060)**; **32222-06-3 (Calcitriol)**; 59865-13-3 (Cyclosporine); 67-97-0 (Cholecalciferol); 7440-70-2 (Calcium)
CN 0 (Drug Combinations); 0 (Immunosuppressive Agents)

L115 ANSWER 5 OF 14 MEDLINE
AN 1998193337 MEDLINE
DN **98193337** PubMed ID: **9532170**
TI Prevention of diabetes recurrence after syngeneic islet transplantation in NOD mice by analogues of 1,25(OH)2D3 in combination with cyclosporin A: mechanism of action involves an immune shift from Th1 to Th2.
AU Mathieu C; Casteels K; Waer M; Laureys J; Valckx D; Bouillon R
CS Legendo and Laboratory for Experimental Transplantation, K.U. Leuven, Belgium.
SO TRANSPLANTATION PROCEEDINGS, (1998 Mar) 30 (2) 541.
Journal code: WE9; 0243532. ISSN: 0041-1345.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980430
Last Updated on STN: 19980430
Entered Medline: 19980422
CT Check Tags: Animal
***Calcitriol: AD, administration & dosage**
*Cyclosporine: AD, administration & dosage
Diabetes Mellitus, Insulin-Dependent: IM, immunology
Diabetes Mellitus, Insulin-Dependent: PP, physiopathology
***Diabetes Mellitus, Insulin-Dependent: SU, surgery**
*Graft Rejection: IM, immunology
*Graft Rejection: PC, prevention & control
*Immunosuppressive Agents: AD, administration & dosage
*Islets of Langerhans Transplantation
Mice
Mice, Inbred NOD
Recurrence
*Th1 Cells: IM, immunology
*Th2 Cells: IM, immunology
Transplantation, Isogeneic
RN **32222-06-3 (Calcitriol)**; 59865-13-3 (Cyclosporine)
CN 0 (Immunosuppressive Agents)

L115 ANSWER 6 OF 14 MEDLINE
AN 97121532 MEDLINE
DN **97121532** PubMed ID: **8962198**
TI Prevention of type I diabetes by late intervention with nonhypercalcemic analogues of vitamin D3 in combination with cyclosporin A.
AU Casteels K; Waer M; Bouillon R; Allewaert K; Laureys J; Mathieu C
CS Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Catholic University of Leuven, Belgium.
SO TRANSPLANTATION PROCEEDINGS, (1996 Dec) 28 (6) 3095.
Journal code: WE9; 0243532. ISSN: 0041-1345.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970121
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Calcitriol: AA, analogs & derivatives
***Calcitriol: TU, therapeutic use**
*Cyclosporine: TU, therapeutic use
Diabetes Mellitus, Insulin-Dependent: PA, pathology
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
Drug Therapy, Combination
*Immunosuppressive Agents: TU, therapeutic use
Islets of Langerhans: DE, drug effects
Islets of Langerhans: PA, pathology
Mice
Mice, Inbred NOD
Stereoisomerism
RN **32222-06-3 (Calcitriol)**; 59865-13-3 (Cyclosporine)
CN 0 (Immunosuppressive Agents)

L115 ANSWER 7 OF 14 MEDLINE
AN 97014668 MEDLINE
DN **97014668** PubMed ID: **8861501**
TI Vitamin D analogues in **insulin**-dependent diabetes mellitus and other autoimmune diseases: a therapeutic perspective.
AU Mauricio D; Mandrup-Poulsen T; Nerup J
CS Steno Diabetes Center, Gentofte, Denmark.
SO DIABETES/METABOLISM REVIEWS, (1996 Apr) 12 (1) 57-68. Ref: 87
Journal code: EAR; 8601109. ISSN: 0742-4221.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970609
Last Updated on STN: 19970609
Entered Medline: 19970527
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
*Autoimmune Diseases: DT, drug therapy
Calcitriol: PD, pharmacology
Cytokines: BI, biosynthesis
***Diabetes Mellitus, Insulin-Dependent: DT, drug therapy**
Immune System: DE, drug effects
Immune System: PH, physiology
Lymphocytes: IM, immunology
Models, Biological
***Vitamin D: AA, analogs & derivatives**
Vitamin D: PD, pharmacology
***Vitamin D: TU, therapeutic use**
RN **1406-16-2 (Vitamin D); 32222-06-3 (Calcitriol)**
CN 0 (Cytokines)

L115 ANSWER 8 OF 14 MEDLINE
AN 96148326 MEDLINE
DN **96148326** PubMed ID: **8571669**
TI [Immune modulation by vitamin D analogs in the prevention of autoimmune diseases].
Immuunmodulatie door vitamine D analogen ter preventie van autoimmune ziekten.
AU Bouillon R; Verstuyf A; Branisteanu D; Waer M; Mathieu C
CS Departement Onderwijs en Navorsing, Universitair Ziekenhuis Gasthuisberg,

Leuven.
SO VERHANDELINGEN - KONINKLIJKE ACADEMIE VOOR GENEESKUNDE VAN BELGIE, (1995) 57 (5) 371-85; discussion 385-7.
Journal code: X8O; 0413210. ISSN: 0302-6469.
CY Belgium
DT Journal; Article; (JOURNAL ARTICLE)
LA Dutch
FS Priority Journals
EM 199603
ED Entered STN: 19960315
Last Updated on STN: 19960315
Entered Medline: 19960307
AB Vitamin D has been discovered at the beginning of this century. 7-Dehydrocholesterol is converted to vitamin D3 in the skin and after several hydroxylations it is further converted to the active hormonal form, 1 alpha,25-(OH)2D3. Vitamin D stimulates the absorption of calcium and phosphate and is an essential link in bone resorption and formation and calcium metabolism. 1 alpha,25-(OH)2D3 acts through a vitamin D receptor. These receptors are not only present in clinical target organs (kidney, gut, liver) but can also be found in a wide variety of "non-classical" tissues (keratinocytes, cells belonging to the immune system). Moreover, numerous cells (keratinocytes, macrophages) can locally synthetize or can be induced to synthetize 1 alpha,25-(OH)2D3 and these cells are responsive to its action. When these data are combined, a possible paracrine function of 1 alpha,25-(OH)2D3 can be suspected. Via this paracrine function 1 alpha,25-(OH)2D3 can suppress the cellular and humoral immunity. Based on the discovery of these effects on immune cells in vitro it became clear that 1 alpha,25-(OH)2D3 might be an interesting molecule to prevent autoimmune diseases and organ transplantation. This has already been shown in several animal models (Heymann nephritis, diabetes mellitus, experimental allergic-encephalomyelitis, lupus). 1 alpha,25-(OH)2D3 demonstrates however some side-effects (hypercalciuria, hypercalcemia, bone resorption) and for this reason 1 alpha,25-(OH)2D3-analogs are developed with dissociated effects i.e. an activity profile that allows a specific action on non-classical tissues without calcemic effects. Some chemical modifications of the side chain, A and/or CD-ring results in "superanalogs" with 10 to 100-fold more activity on cell differentiation and the immune system then 1 alpha,25-(OH)2D3 but with less calcemic activity in vivo. These biological effects can be explained by differences in pharmacokinetics (low affinity for the plasma vitamin D-binding protein and short extracellular half-life) and increased intracellular activation and gen transactivation. Preclinical research must still be done to select the most potent superanalogs and to find the exact protocols for the prevention and treatment of autoimmune diseases and rejection of transplanted organs.
CT Check Tags: Animal; Human
*Autoimmune Diseases: PC, prevention & control
Calcium: ME, metabolism
Diabetes Mellitus, Experimental: IM, immunology
Diabetes Mellitus, Experimental: PC, prevention & control
Graft Rejection: IM, immunology
Hydroxycholecalciferols: CH, chemistry
Hydroxycholecalciferols: PD, pharmacology
***Hydroxycholecalciferols: TU, therapeutic use**
Immune System: DE, drug effects
Mice
Mice, Inbred NOD
Vitamin D: PD, pharmacology
***Vitamin D: TU, therapeutic use**
RN **1406-16-2 (Vitamin D)**; 7440-70-2 (Calcium)
CN 0 (Hydroxycholecalciferols)

L115 ANSWER 9 OF 14 MEDLINE
AN 95172016 MEDLINE
DN **95172016** PubMed ID: **7867594**
TI Prevention of type I diabetes in NOD mice by nonhypercalcemic doses of a

new structural analog of 1,25-dihydroxyvitamin D3, KH1060.
AU Mathieu C; Waer M; Casteels K; Laureys J; Bouillon R
CS Laboratory for Experimental Medicine and Endocrinology, Catholic University of Leuven, Belgium.
SO ENDOCRINOLOGY, (1995 Mar) 136 (3) 866-72.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199503
ED Entered STN: 19950407
Last Updated on STN: 19950407
Entered Medline: 19950329
AB Pharmacological amounts of 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] have potent immunoregulatory activity, but with marked effects on calcium and bone metabolism. In this study we demonstrate that nonhypercalcemia-inducing nondemineralizing doses of an analog of 1,25-(OH)2D3, 1 alpha,25-(OH)2-20-epi-22-oxa-24,26,27-trishomo-vitamin D (KH1060), can prevent type I diabetes. Female NOD mice received 1,25-(OH)2D3 (5 micrograms/kg), KH1060 (0.4 or 0.2 micrograms/kg), or the treatment vehicle ip every 2 days from 21-200 days of age. The incidence of diabetes in controls was 17 of 31 (55%), whereas 7 of 38 (18%) 1,25-(OH)2D3-treated mice, 3 of 27 (11%) KH1060 (0.4 micrograms/kg)-treated mice, and 6 of 27 (22%) KH1060 (0.2 micrograms/kg)-treated mice developed diabetes ($P < 0.025$ vs. controls). Protection was achieved with the low KH1060 dose without effects on calcium or bone metabolism, as evaluated by serum calcium (9.5 +/- 0.4 vs. 9.4 +/- 0.3 mg/dl in controls; P = NS), serum osteocalcin (82 +/- 17 vs. 83 +/- 20 ng/ml; P = NS), bone calcium content (6.8 +/- 0.7 vs. 6.4 +/- 0.5 mg/tibia; P = NS), urinary calcium (21 +/- 4 vs. 21 +/- 4 mg/dl; P = NS), pyridinoline excretion, and duodenal calbindin-D9K concentration. The proposed mechanism of action is a restoration of suppressor cell activity, as demonstrated in vitro (suppressor cell assay) and in vivo (cell transfer experiments). This study demonstrates that an analog of 1,25-(OH)2D3 prevents type I diabetes in NOD mice without significant effects on calcium or bone metabolism.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
***Calcitriol: AA, analogs & derivatives**
Calcitriol: PD, pharmacology
Cell Count
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
Hypercalcemia: CI, chemically induced
Immunization, Passive
Immunosuppressive Agents: PD, pharmacology
Islets of Langerhans: DE, drug effects
Mice
Mice, Inbred NOD
Pancreatitis: PC, prevention & control
T-Lymphocytes, Suppressor-Effector: PA, pathology
RN **131875-08-6 (KH 1060); 32222-06-3 (Calcitriol)**
CN 0 (Immunosuppressive Agents)

L115 ANSWER 10 OF 14 MEDLINE
AN 95090690 MEDLINE
DN **95090690** PubMed ID: **7998092**
TI Prevention of autoimmune destruction of transplanted islets in spontaneously diabetic NOD mice by KH1060, a 20-epi analog of vitamin D: synergy with cyclosporine.
AU Mathieu C; Laureys J; Waer M; Bouillon R
CS Laboratory for Experimental Medicine and Endocrinology, K.U. Leuven, Belgium.
SO TRANSPLANTATION PROCEEDINGS, (1994 Dec) 26 (6) 3128-9.
Journal code: WE9; 0243532. ISSN: 0041-1345.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 199501
ED Entered STN: 19950126
Last Updated on STN: 19950126
Entered Medline: 19950118
CT Check Tags: Animal; Support, Non-U.S. Gov't
***Calcitriol: AA, analogs & derivatives**
Calcitriol: TU, therapeutic use
*Cyclosporine: TU, therapeutic use
***Diabetes Mellitus, Insulin-Dependent: TH, therapy**
Drug Synergism
*Graft Survival: DE, drug effects
Graft Survival: IM, immunology
*Immunosuppressive Agents: TU, therapeutic use
*Islets of Langerhans Transplantation: IM, immunology
Mice
Mice, Inbred NOD
Time Factors
Transplantation, Isogeneic
RN **131875-08-6 (KH 1060); 32222-06-3 (Calcitriol);**
59865-13-3 (Cyclosporine)
CN 0 (Immunosuppressive Agents)

L115 ANSWER 11 OF 14 MEDLINE
AN 95011108 MEDLINE
DN **95011108** PubMed ID: **7926338**
TI Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D3.
AU Mathieu C; Waer M; Laureys J; Rutgeerts O; Bouillon R
CS Laboratory for Experimental Medicine and Endocrinology, Catholic University of Leuven, Belgium.
SO DIABETOLOGIA, (1994 Jun) 37 (6) 552-8.
Journal code: E93; 0006777. ISSN: 0012-186X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199410
ED Entered STN: 19941222
Last Updated on STN: 19970203
Entered Medline: 19941025
AB 1,25 dihydroxyvitamin D3, the active form of vitamin D, has immunomodulatory properties in vitro and in vivo. We report that treatment with 1,25 dihydroxyvitamin D3 (5 micrograms/kg on alternate days) prevents the development of clinical diabetes in NOD mice, an animal model of human autoimmune diabetes. Diabetes incidence in female NOD mice at the age of 200 days was reduced to 8% in the 1,25 dihydroxyvitamin D treated group vs 56% in the control group ($p < 0.0001$). In parallel, treatment with 1,25 dihydroxy-vitamin D3 resulted in a complete normalisation of the capacity to induce suppressor mechanisms in an autologous MLR, which is severely depressed in control NOD mice. The existence of such suppressor cells was confirmed in transfer experiments, whereby cotransfer of splenocytes from 1,25 dihydroxyvitamin D3 treated NOD mice prevented diabetes transfer by splenocytes from diabetic NOD mice into irradiated, 6-8-week-old male NOD mice. Other known immune defects of the NOD mice, such as defective natural killer cell killing of YAC-1 targets and defective thymocyte activation by anti-CD3 were not corrected. The pharmacological doses of 1,25 dihydroxyvitamin D3 were universally well tolerated as reflected by a normal weight gain of the mice. Serum calcium was increased (2.5 +/- 0.2 vs 2.2 +/- 0.2 mmol/l in the control group, $p < 0.005$), whereas osteocalcin levels nearly doubled and bone calcium content was halved. These findings show that 1,25 dihydroxyvitamin D3 can prevent diabetes in NOD mice, probably through the correction of their defective suppressor function.
CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't
Calcitriol: AD, administration & dosage
***Calcitriol: TU, therapeutic use**

Calcium: ME, metabolism
Diabetes Mellitus, Insulin-Dependent: IM, immunology
Diabetes Mellitus, Insulin-Dependent: ME, metabolism
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
*Immunotherapy, Adoptive
Insulin: ME, metabolism
Killer Cells, Natural: IM, immunology
Lymphocyte Culture Test, Mixed
Lymphocyte Transformation: IM, immunology
Mice
Mice, Inbred C3H
Mice, Inbred C57BL
Mice, Inbred NOD
T-Lymphocytes, Suppressor-Effector: IM, immunology
RN **11061-68-0 (Insulin); 32222-06-3 (Calcitriol);**
7440-70-2 (Calcium)

L115 ANSWER 12 OF 14 MEDLINE
AN 93092868 MEDLINE
DN **93092868** PubMed ID: **1459048**
TI Clinical counterpoint: vitamin D: new actions, new analogs, new therapeutic potential.
AU Bikle D D
CS Endocrine Research Unit, Veterans Administration Medical Center, San Francisco, California 94121.
NC AR-38386 (NIAMS)
AR-39448 (NIAMS)
SO ENDOCRINE REVIEWS, (1992 Nov) 13 (4) 765-84. Ref: 264
Journal code: EIK; 8006258. ISSN: 0163-769X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199301
ED Entered STN: 19930129
Last Updated on STN: 19930129
Entered Medline: 19930108
CT Check Tags: Animal; Human; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Bone Diseases: DT, drug therapy
Calcitriol: AA, analogs & derivatives
Calcitriol: CH, chemistry
Calcitriol: PH, physiology
Calcitriol: TU, therapeutic use
Diabetes Mellitus: DT, drug therapy
Hypertension: DT, drug therapy
Immunity
Neoplasms: DT, drug therapy
Psoriasis: DT, drug therapy
***Vitamin D**
Vitamin D: AA, analogs & derivatives
Vitamin D: CH, chemistry
Vitamin D: PH, physiology
Vitamin D: TU, therapeutic use
RN **1406-16-2 (Vitamin D); 32222-06-3 (Calcitriol)**

L115 ANSWER 13 OF 14 MEDLINE
AN 92200785 MEDLINE
DN **92200785** PubMed ID: **1666347**
TI Changes of vitamin D3 serum concentrations at the onset of immune-mediated type 1 (**insulin**-dependent) diabetes mellitus.
AU Baumgartl H J; Standl E; Schmidt-Gayk H; Kolb H J; Janka H U; Ziegler A G
CS Diabetes Research Institute, Heidelberg, FRG.
SO DIABETES RESEARCH, (1991 Mar) 16 (3) 145-8.

Journal code: DIA; 8502339. ISSN: 0265-5985.
CY SCOTLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199204
ED Entered STN: 19920509
Last Updated on STN: 19920509
Entered Medline: 19920428
AB Several hormones such as 1,25-dihydroxy-vitamin D3 (1,25-(OH)2D3), alpha-MSH, or ACTH have been found to interact extensively with the immune system. In view of the immune-mediated nature of Type 1 (**insulin** -dependent) diabetes mellitus, 49 recently diagnosed diabetic patients were investigated in terms of serum 1,25-(OH)2D3-levels, 25-hydroxyvitamin D3(25-(OH)D3), alpha-MSH and ACTH, and compared with 42 healthy controls. A marked decrease of 1,25-(OH)2D3-levels was found at onset of Type 1 (**insulin**-dependent) diabetes compared to normal controls (39 +/- 2 vs 55 +/- 4 pg/ml, p less than 0.01). Grouping patients according to season (winter or summer) of diabetes onset and blood sampling, it was demonstrated that the decrease of 1,25-(OH)2D3 was primarily present during summer and due to a loss of the seasonal rhythm of this hormone observed in healthy controls (summer: patients vs controls 41 +/- 2 vs 63 +/- 4 pg/ml, p less than 0.001; winter: 37 +/- 3 vs 33 +/- 3 pg/ml, n.s.). Serum concentrations of 25-(OH)D3 were closely correlated with those of 1,25-(OH)2D3, both in controls (r = 0.55, p less than 0.002) and diabetic patients (r = 0.41, p less than 0.05), yielding a similar loss of seasonal variation also of this vitamin D3 metabolite in Type 1 (**insulin** -dependent) diabetic patients. No difference was found in the mean and median values of alpha-MSH and ACTH between IDDM patients and controls, although patients exhibited much higher variation of alpha-MSH levels than did controls.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Comparative Study; Female; Human; Male; Support, Non-U.S. Gov't
Adult
***Calcitriol: BL, blood**
Corticotropin: BL, blood
***Diabetes Mellitus, Insulin-Dependent: BL, blood**
Radioimmunoassay
Reference Values
Time Factors
alpha-MSH: BL, blood
RN **32222-06-3 (Calcitriol)**; 581-05-5 (alpha-MSH); 9002-60-2 (Corticotropin)

L115 ANSWER 14 OF 14 MEDLINE
AN 89247974 MEDLINE
DN **89247974** PubMed ID: **3334207**
TI Effect of 1 alpha (OH)-vitamin D3 on **insulin** secretion in diabetes mellitus.
AU Inomata S; Kadowaki S; Yamatani T; Fukase M; Fujita T
CS Department of Internal Medicine, Kobe Teishin Hospital, Japan.
SO BONE AND MINERAL, (1986 Jun) 1 (3) 187-92.
Journal code: BMI; 8610542. ISSN: 0169-6009.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198906
ED Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890623
AB Fourteen non-**insulin**-dependent diabetic subjects were placed on a balanced diet for 2-3 weeks followed by the same balanced diet alone (group I: control, n = 7) or daily administration of 1 alpha (OH)-vitamin D3 (1 alpha (OH)D3) (group II: 2 micrograms/day, n = 7) additionally for the next 3 weeks. A 75 g oral **glucose** loading test was conducted

ordered 10-1-01

before and after the experiment and the plasma **insulin** response was compared along with the metabolic parameters including serum calcium, phosphorus and serum lipids. The following results were obtained. (1) Total **insulin** secretion in response to 75 g **glucose** loading was significantly increased in group II (16.3 +/- 3.9 microU/2 h/ml versus 22.7 +/- 4.9 microU/2 h/ml; P less than 0.05), though no difference was demonstrated in group I. (2) Mean serum calcium level was significantly increased from 9.4 +/- 0.1 mg/dl to 9.6 +/- 0.1 mg/dl (P less than 0.05) and serum free fatty acid level was decreased from 0.80 +/- 0.07 mEq/l to 0.53 +/- 0.07 mEq/l (P less than 0.05) in group II, but not in group I. (3) However, there was no direct correlation between total **insulin** secretion during a 75 g oral **glucose** loading test and serum calcium or free fatty acid level. The findings that 1 alpha (OH)D3 enhances **insulin** secretion and reduces the levels of serum free fatty acid in non-**insulin**-dependent diabetics provide us with the possibility that vitamin D may play some role in the regulation of **insulin** secretion.

CT Check Tags: Female; Human; Male
Adult
Aged
Aged, 80 and over
Blood Glucose: ME, metabolism
Calcium: BL, blood
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Diabetes Mellitus, Non-Insulin-Dependent: PP, physiopathology
***Hydroxycholecalciferols: TU, therapeutic use**
***Insulin: SE, secretion**
Middle Age

RN **11061-68-0 (Insulin); 41294-56-8 (1-hydroxycholecalciferol)**; 7440-70-2 (Calcium)

CN 0 (Blood **Glucose**); 0 (Hydroxycholecalciferols)

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FILE LAST UPDATED: 10 SEP 2001 <20010910/UP>
MOST RECENT DERWENT UPDATE 200151 <200151/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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L146 ANSWER 1 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-365091 [31] WPIX
DNC C2000-110162
TI New **vitamin D3** derivatives used for treating e.g. inflammatory respiratory conditions, tumors, **diabetes** and hypertension.
DC B01 B05
IN GAO, Q; ISHIZUKA, S; MANABE, K; SOGAWA, R; TAKANO, Y; TAKENOUCHI, K
PA (TEIJ) TEIJIN LTD
CYC 91
PI WO 2000024712 A1 20000504 (200031)* JA 145p C07C401-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 9962281 A 20000515 (200039) C07C401-00
EP 1123921 A1 20010816 (200147) EN C07C401-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI

ADT WO 2000024712 A1 WO 1999-JP5826 19991022; AU 9962281 A AU 1999-62281 19991022; EP 1123921 A1 EP 1999-949355 19991022, WO 1999-JP5826 19991022

FDT AU 9962281 A Based on WO 200024712; EP 1123921 A1 Based on WO 200024712

PRAI JP 1998-365209 19981222; JP 1998-302321 19981023; JP 1998-362827 19981221; JP 1998-365207 19981222; JP 1998-365208 19981222

IC ICM C07C401-00
ICS A61K031-59; A61P003-02; A61P003-14; A61P011-00; C07F007-18

AB WO 200024712 A UPAB: 20000630
NOVELTY - **Vitamin D3** derivatives (I) are new.
DETAILED DESCRIPTION - **Vitamin D3** derivatives of formula (I) and their hydrates are new.
R1, R2 = H, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, acetyl, methoxymethyl or tetrahydro-4H-pyran-2-yl;
Z = (CH2)3C(OH)R51R52 or a group of formula (i) -(iv);
m, n = 0-2;
X1 = O or NH;
K-M = H or
K + L or L + M = a bond;
R21-R22, R31, R43-R46 = H, OH, COOH, CF3, C2F5, 1-4C alkoxycarbonyl 2-5C acyloxy, 1-4C alkoxy or 1-4C alkyl (optionally substituted by OH, 2-5C acyloxy or 1-4C alkoxy), or
CR21R22, CR41R42 and/or CR43R44 = 3-6C cycloalkyl;
Q = CFR31 or NR31;
R32-R35 = H, OH, 1-4C alkyl or 2-5C acyloxy;
A, B = H or OH or
A + B = a bond;
CXY = CO, or
one of X and Y = H and
the other = OH or 2-5C acyloxy;
D, E = H or
D = OH and
E = H or
D + E = a bond, or
E + R41 = a bond and
D = H or OH;
R51 = CONR51R512, COR513 or C(OH)R514R515;
R511, R512 = H or 1-4C alkyl or
NR511R512 = 3-8C saturated heterocyclyl or morpholino;
R513-R515 = 1-4C alkyl and
R52 = Me, Et, CF3 or C2F5,
provided that:
(1) R21 and R22, R32 and R33, R34 and R35, R41 and R42, R43 and R44, R45 and R46 are not both OH and/or alkoxy;
(2) Z is not a group of formula (v) in which p and q are 0 or 1 and R6 is H or 1-4C alkyl and
(3) when Z = a group of formula (vi) then the group in the 20 position is (R) and R7 = methyl or methylene.
ACTIVITY - Antiinflammatory; respiratory-Gen.; antiallergic; antiasthmatic; cytostatic; antirheumatic; osteopathic; antidiabetic; hypotensive; endocrine-Gen.; antiseborrheic; dermatological; antipsoriatic; muscular-Gen.
In the lipopolysaccharide induced bronchitis model in hamsters compound of formula (Ia) at 4 mu g/kg suppressed eosinophil production by greater than 40% (no specific values are given).
MECHANISM OF ACTION - None given.
USE - For treating and preventing inflammatory respiratory conditions

(such as acute bronchial congestion, chronic hayfever, allergic rhinitis, pulmonary emphysema, pneumonia and chronic asthma), malignant tumor, articular rheumatism, osteoporosis, diabetes mellitis, hypertension, alopecia, acne, psoriasis, dermatitis, hypercalcemia, hyperactive thyroid gland or cartilage metabolic disorders (claimed).
Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: **B03-G**; B14-A01A4; B14-C03; B14-C06; B14-G02A; B14-H01; B14-K01; B14-K01A; B14-N01; B14-N04; B14-N11; B14-N17C; B14-N17D; B14-R02; **B14-S04**
TECH UPTX: 20000630
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared e.g. by reacting a bicyclo compound of formula (IV) with a enzyme compound of formula (V) in the presence of palladium.
Y = Br or I.

L146 ANSWER 2 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-277033 [23] WPIX
DNC C1999-081298
TI New 1alpha,25-Dihydroxyvitamin D3 analogs for treatment of **endocrine** disorders.
DC B01 B05
IN NORMAN, A W; OKAMURA, W H
PA (REGC) UNIV CALIFORNIA; (NORM-I) NORMAN A W; (OKAM-I) OKAMURA W H
CYC 83
PI WO 9916452 A1 19990408 (199923)* EN 177p A61K031-595
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9895035 A 19990423 (199935)
EP 1021193 A1 20000726 (200037) EN A61K031-595
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6103709 A 20000815 (200041) C07C401-00
US 6121469 A 20000919 (200048) C07C401-00
US 2001014749 A1 20010816 (200149) C07C401-00
ADT WO 9916452 A1 WO 1998-US19862 19980923; AU 9895035 A AU 1998-95035 19980923; EP 1021193 A1 EP 1998-948468 19980923, WO 1998-US19862 19980923; US 6103709 A Cont of US 1993-173561 19931223, CIP of US 1994-249385 19940525, CIP of US 1995-558717 19951116, CIP of US 1996-706356 19960830, Provisional US 1997-60173 19970926, US 1998-73723 19980507; US 6121469 A Cont of US 1993-173561 19931223, CIP of US 1994-249385 19940525, CIP of US 1995-558717 19951116, CIP of US 1996-706356 19960830, Provisional US 1997-60173 19970929, US 1998-74565 19980507; US 2001014749 A1 CIP of US 1993-173561 19931223, CIP of US 1994-249385 19940525, CIP of US 1995-558717 19951116, CIP of US 1996-706356 19960830, Provisional US 1997-60173 19970926, Div ex US 1998-74565 19980507, US 1999-452282 19991130
FDT AU 9895035 A Based on WO 9916452; EP 1021193 A1 Based on WO 9916452; US 2001014749 A1 Div ex US 6121469
PRAI US 1998-74565 19980507; US 1997-60173 19970926; US 1998-73723 19980507; US 1993-173561 19931223; US 1994-249385 19940525; US 1995-558717 19951116; US 1996-706356 19960830; US 1999-452282 19991130
IC ICM A61K031-595; C07C401-00
ICS A61K031-59; C07C403-00
AB WO 9916452 A UPAB: 19990616
NOVELTY - New 1 alpha ,25-Dihydroxyvitamin D3 analogs (I).
DETAILED DESCRIPTION - 1 alpha ,25-Dihydroxyvitamin D3 analogs of formula (I)-(V) and their salts are new.
In (I):
R1 = Me or OH;
C5-C6 and C7-C8 double bonds = cis or trans;

C16-C17 bond = a single or double bond and
R2, R1' = a group of formula (i)-(x);
provided that:
in (I):
(1) when R1 is Me and when C1 and C3 are approx. a- approx. b, then R2 is not (i)-(iii), (ix) or (x);
(2) when C1 is alpha and C3 is beta , C5-C6 is cis or trans and C7-C8 is trans, R1 is Me, C14 H is in the alpha orientation and C16-C17 is a single or double bond, then R2 is not (i)-(v), (ix) or (x);
(3) when C1 is alpha , C3 is beta , C5-C6 is cis, C7-C8 is trans, R1 is CH2OH, C14 H is alpha and C16-C17 is a single bond then R2 is not (i);
(4) when C3 is approx. b, C1 is not OH, C5-C6 is cis, C7-C8 is trans, R1 is Me, C14 H is alpha and C16-C17 is a single bond, then R2 is (vii) or (viii) and
(5) when C3 is approx. b, C1 is alpha , C5-C6 is cis, C7-C8 is trans, R1 is Me, C14 H is alpha and C16-C17 is a single bond, then R2 is a modified version of side chain (vi) where the C22 methylene is replaced by a carbon-carbon triple bond.
In (II):
when C1 and C3 are alpha - beta , C9 and C10 are in any configuration and C16-C17 is a single bond, then R1' is not (i).
In (III):
(A) when C1 and C3 hydroxyls are alpha - beta , C14 H is alpha and C16-C17 is a single bond, then R1' is not (i)-(iii), (ix) or (x) and
(B) when C1 and C3 hydroxyls are alpha - beta and C14 H is alpha and C16-C17 is a single or double bond, then R1' is not (iv) or (v).
In (IV):
C14 H = alpha ;
In (V):
C5-C6 double is cis and C7-C8 double bond is trans.
ACTIVITY - None given.
MECHANISM OF ACTION - **Vitamin D3**-receptor VDRnuc or VDRmem agonists or antagonists.
USE - Used for treatment of diseases of the endocrine system, particularly diseases connected with or caused by **vitamin D3** deficiency or overproduction (claimed) including rickets, osteomalacia, osteoporosis, osteopenia, osteosclerosis, renal osteodystrophy, psoriasis, medullary carcinoma, Alzheimer's disease, hyperparthyroidism, hypoparathyroidism, pseudoparathyroidism, secondary parathyroidism, pseudoparathyroidism, secondary parathyroidism, **diabetes**, cirrhosis, obstructive jaundice or drug-induced metabolism, glucocorticoid antagonism, hypercalcemia, malabsorption syndrome, steatorrhoea, chronic renal disease, hypophosphatemic **vitamin D**-resistant rickets, **vitamin D**-dependent rickets, rickets type I, rickets type II sarcoidosis, leukemia, prostate cancer, breast cancer, colon cancer, organ transplant or immunodisorder.
Dwg.0/15

FS CPI
FA AB; GI; DCN
MC CPI: B14-E11; B14-G01; B14-H01; B14-H01A; B14-J01A4; B14-L01; B14-L06; B14-N01; B14-N07; B14-N12; B14-N17C; **B14-S04**
TECH UPTX: 19990616
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared by reacting a compound of formula (XX) with isooctane under reflux.
(II) are prepared by reacting a compound of formula (XXI) with a base in dimethylformamide.
(III) are prepared by reacting a compound (XXII) with e.g. NaBH4 or NaBH(OAc)3 in methanol.
(IV) are prepared by irradiating (XXIII) in methanol.

TECHNOLOGY FOCUS - PHARMACEUTICALS - The analogue is a conformationally flexible or restricted agonist or antagonist.

L146 ANSWER 3 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-105584 [09] WPIX

DNC C1999-031419
TI New **vitamin D** derivatives - for treating inflammatory respiratory diseases, malignant tumours, articular rheumatism, osteoporosis, **diabetes** mellitus, hypertension, baldness, acne, psoriasis and dermatitis.
DC B05
IN CHOKKI, M; FURUYA, M; GAO, Q; HAZATO, A; ISHIZUKA, S; KISHIMOTO, T; MANABE, K; MITSUHASHI, H; SAKUMA, Y; TABE, M; TANAKA, H
PA (TEIJ) TEIJIN LTD
CYC 25
PI WO 9858909 A1 19981230 (199909)* JA 117p C07C401-00
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA CN JP KR US
AU 9879328 A 19990104 (199921) C07C401-00
EP 970948 A1 20000112 (200008) EN C07C401-00
R: AT BE CH DE ES FR GB IT LI NL SE
JP 11504175 X 19991207 (200008) C07C401-00
CN 1236360 A 19991124 (200014) C07C401-00
US 6028208 A 20000222 (200017) C07C401-00
KR 2000068317 A 20001125 (200130) C07C401-00
ADT WO 9858909 A1 WO 1998-JP2813 19980624; AU 9879328 A AU 1998-79328 19980624; EP 970948 A1 EP 1998-929661 19980624, WO 1998-JP2813 19980624; JP 11504175 X WO 1998-JP2813 19980624, JP 1999-504175 19980624; CN 1236360 A CN 1998-801176 19980624; US 6028208 A WO 1998-JP2813 19980624, US 1999-242665 19990222; KR 2000068317 A WO 1998-JP2813 19980624, KR 1999-701474 19990224
FDT AU 9879328 A Based on WO 9858909; EP 970948 A1 Based on WO 9858909; JP 11504175 X Based on WO 9858909; US 6028208 A Based on WO 9858909; KR 2000068317 A Based on WO 9858909
PRAI JP 1997-168803 19970625
IC ICM C07C401-00
ICS A61K031-59
AB WO 9858909 A UPAB: 19990302
Vitamin D derivatives of formula (I) and their solvates are new: Z = a group of formula (a)-(c): R1, R2 = H, tri(1-7C alkyl)silyl, acetyl, methoxymethyl or tetrahydrofuryl; R3, R4 = H, OH, 2-8C acyloxy, 1-7C alkoxy, 1-6C alkylthio or 1-7C alkyl (optionally substituted by OH, 2-8C acyloxy or 1-7C alkoxy); R5-R8 = H, OH, 1-7C alkyl or 2-8C acyloxy; R9 = H, OH, 1-7C alkyl or 1-6C alkylthio; R10 = H, 1-7C alkyl or 1-7C alkoxy; A, B = H or OH; or A+B = a bond; one of X and Y = H the other =OH or 2-7C acyloxy; or CXY = CO; n, m = 0-2.
USE - (I) are useful for the treatment and prophylaxis of inflammatory respiratory diseases (e.g. allergic rhinitis, asthma and bronchitis), malignant tumours, articular rheumatism, osteoporosis, **diabetes** mellitus, hypertension, baldness, acne, psoriasis and dermatitis.
Dwg.0/3
FS CPI
FA AB; GI; DCN
MC CPI: **B03-G**; B14-C03; B14-C06; B14-F02B; B14-H01; B14-K01; B14-N01; B14-N17C; B14-N17D; B14-R02; **B14-S04**

L146 ANSWER 4 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1997-558535 [51] WPIX
DNC C1997-178256
TI New **vitamin D** analogues - useful for treating hyperparathyroidism, osteoporosis, neurological dysfunction and **diabetes** mellitus, and for promoting osteogenesis.
DC B05
IN GRUE-SORENSEN, G; GRUESORENSEN, G
PA (LOVE) LEO PHARM PROD LTD
CYC 77
PI WO 9737972 A1 19971016 (199751)* EN 56p C07C401-00
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE

HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX
NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU

AU 9725670	A	19971029 (199810)			C07C401-00
CZ 9800008	A3	19980617 (199830)			C07C401-00
EP 891326	A1	19990120 (199908)	EN		C07C401-00
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CN 1196720	A	19981021 (199910)			C07C401-00
US 5932565	A	19990803 (199937)			A61K031-59
HU 9901600	A2	19990928 (199946)			C07C401-00
AU 713630	B	19991209 (200009)			C07C401-00
KR 99035844	A	19990525 (200032)			C07C401-00
JP 2000508635 W		20000711 (200038)		55p	C07C401-00
NZ 329531	A	20010330 (200121)			A61K031-59
RU 2169142	C2	20010620 (200144)			C07C401-00

ADT WO 9737972 A1 WO 1997-DK128 19970321; AU 9725670 A AU 1997-25670 19970321; CZ 9800008 A3 WO 1997-DK128 19970321, CZ 1998-8 19970321; EP 891326 A1 EP 1997-917272 19970321, WO 1997-DK128 19970321; CN 1196720 A CN 1997-190740 19970321; US 5932565 A WO 1997-DK128 19970321, US 1998-983293 19980114; HU 9901600 A2 WO 1997-DK128 19970321, HU 1999-1600 19970321; AU 713630 B AU 1997-25670 19970321; KR 99035844 A WO 1997-DK128 19970321, KR 1998-700504 19980123; JP 2000508635 W JP 1997-535756 19970321, WO 1997-DK128 19970321; NZ 329531 A NZ 1997-329531 19970321, WO 1997-DK128 19970321; RU 2169142 C2 WO 1997-DK128 19970321, RU 1998-119976 19970321

FDT AU 9725670 A Based on WO 9737972; CZ 9800008 A3 Based on WO 9737972; EP 891326 A1 Based on WO 9737972; US 5932565 A Based on WO 9737972; HU 9901600 A2 Based on WO 9737972; AU 713630 B Previous Publ. AU 9725670, Based on WO 9737972; KR 99035844 A Based on WO 9737972; JP 2000508635 W Based on WO 9737972; NZ 329531 A Based on WO 9737972; RU 2169142 C2 Based on WO 9737972

PRAI GB 1996-7034 19960403

REP 2.Jnl.Ref; EP 521550; EP 619304

IC ICM A61K031-59; C07C401-00
ICS A61K031-00; A61P003-02; A61P003-10; A61P009-12; A61P017-06; A61P017-10; A61P017-14; A61P019-10; A61P025-28; A61P029-00; A61P035-00; A61P037-02; C07C041-26; C07C043-13

ICA C07D309-12; C07F007-18

AB WO 9737972 A UPAB: 19971222

Vitamin D analogues of formula (I) are new. Q = divalent 1-8C hydrocarbylene; R = H or 1-6C hydrocarbyl; or R-C-R = 3-8C carbocyclic ring.

USE - (I) are useful for treatment and prophylaxis of hyperparathyroidism, osteoporosis, neurological dysfunctions (e.g. Alzheimer's disease), **diabetes** mellitus, hypertension, acne, alopecia, skin ageing, imbalance of the immune system, inflammatory diseases (e.g. rheumatoid arthritis and asthma) and diseases characterised by abnormal cell differentiation and proliferation (e.g. psoriasis and cancer) and for promoting osteogenesis.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: **B03-G**; B14-C09B; B14-F02B; B14-G03; B14-H01; B14-J01; B14-K01A; B14-N01; B14-N11; B14-N17C; B14-N17D; B14-R02; **B14-S04**

L146 ANSWER 5 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1997-469492 [43] WPIX

DNC C1997-149098

TI Method of modulating immune system - by administering **vitamin D** especially for treating auto-immune **diabetes**.

DC B01 B04 B05 C03

IN BOUILLON, R; MATHIEU, C; WAER, M

PA (KULE-N) KU LEUVEN RES & DEV

CYC 1

PI US 5665387	A	19970909 (199743)*		11p	A61K009-20

ADT US 5665387 A US 1994-299936 19940901

PRAI US 1994-299936 19940901

IC ICM A61K009-20
AB US 5665387 A UPAB: 19971119
Method for modulating the immune system of a subject comprises administering 0.1 mu g/kg to 1 mg/kg of a **vitamin D** compound of formula (I) or an alkyl, aryl, alkenyl, alkynyl, fluoro, thio, cycloalkyl, epoxy, hydroxy or keto derivative of it. X = H or OH; Y = H or F; Z = H or 1-4C alkyl; W = H; W' = H or Me; W+W' = =CH2; R = a group of formula (i) where one or more C atoms may be replaced by O or S; and n = < 3.
USE - The composition is useful for up-regulating the suppressor arm of the immune system, especially for treating autoimmune **diabetes** (claimed). They are also useful for retarding or blocking rejection of transplanted beta cells, or beta cell containing tissues, like islets of Langerhans.
Dwg.0/6
FS CPI
FA AB; GI; DCN
MC CPI: **B03-G**; **C03-G**; B14-G02C; C14-G02C; B14-G02D; C14-G02D

L146 ANSWER 6 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1995-140315 [19] WPIX
DNC C1995-064794
TI New 2-halo-1,25-di hydroxy-**cholecalciferol** derivs. - are cell proliferation inhibitors and cell differentiation inducers, useful in treating e.g. **diabetes**, hypertension, asthma and cancer.
DC B01 B05
IN GLIESING, S; REICHENBAECHER, M; SCHOENECKER, B
PA (SCHD) SCHERING AG
CYC 1
PI DE 4334154 A1 19950406 (199519)* 8p C07C401-00
DE 4334154 C2 19970522 (199725) 6p C07C401-00
ADT DE 4334154 A1 DE 1993-4334154 19931001; DE 4334154 C2 DE 1993-4334154 19931001
PRAI DE 1993-4334154 19931001
IC ICM C07C401-00
ICS A61K031-59
AB DE 4334154 A UPAB: 19950524
2-Halo-1,25-dihydroxy-**cholecalciferols** of formula (I) are new: X = Cl or Br; R1 = H, 1-9C alkanoyl, or benzoyl. Also claimed are diastereomers of (I) and their mixts.
USE - (I) induce cell differentiation and inhibit undesired cell proliferation; (I) are useful for treating diseases related to abnormal cell differentiation and/or cell proliferation, e.g. psoriasis and cancer; (I) is useful in treating and preventing **diabetes** mellitus, hypertension, immune disorders and inflammatory disorders, e.g. rheumatoid arthritis and asthma; and (I) is useful in preventing transplant rejection; all claimed. (I) also have typical **vitamin D** activity and may thus be used to regulate calcium and phosphate metabolism.
ADVANTAGE - Compared with calcitriol, (I) have higher affinity to calcitriol receptors and an improved cell differentiation induction. Further, (I;R1 = H) have a more pronounced **vitamin D** activity than the corresp. 2beta-fluoro cpd. known from US4307025.
Dwg.0/1
FS CPI
FA AB; DCN
MC CPI: **B03-G**; B14-F02B; B14-H01; B14-K01A; **B14-S04**

L146 ANSWER 7 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1995-067666 [10] WPIX
DNC C1995-029926
TI New **vitamin D** cpds. - useful in treatment of, e.g., cancer, **diabetes**, psoriasis or transplant rejection.
DC B01 B05 D21 E15
IN DIJKSTRA, G D H; HALKES, S J; MASCARENAS, J; MOURINO, A; SESTELO, J P;

VAN, DE VELDE J; ZORGDRAGER, J
PA (DUIN) DUPHAR INT RES BV
CYC 2
PI CA 2097997 A 19941209 (199510)* 38p C07C401-00
JP 07017947 A 19950120 (199513)# 26p C07C401-00
ADT CA 2097997 A CA 1993-2097997 19930608; JP 07017947 A JP 1993-185478 19930629
PRAI CA 1993-2097997 19930608
IC ICM C07C401-00
ICS A61K007-48; A61K031-59; A61K049-00; C07C049-513; C07D303-14; C07F007-18
AB CA 2097997 A UPAB: 19950314
Vitamin D cpds. of formula (I) are new: R1 = H or OH; R2 = 1-3C alkyl, hydroxy(1-3C)alkyl, 1-2C alkoxymethyl, 2-3C alkenyl or 2-3C alkynyl; R3 = an opt. branched, opt. unsatd., aliphatic 3-5 membered hydrocarbon or oxahydrocarbon biradical, contg. at least 3 atoms in the main chain and being opt. substd. by one or more epoxy, fluoro and/or OH gp.; R4 = H or Me; or A + B = CH2.
(I) are useful in treatment of **diabetes**, inflammatory diseases, osteoporosis, renal osteodystrophy, osteomalacia, skin disorders (e.g. psoriasis, eczema, dermatitis, etc.), myopathy, leukaemia, breast and colon cancer, osteosarcomas, squamous cell carcinomas, melanoma, transplant rejections and immunological disorders. They may also be used for wound healing and may be incorporated in cosmetic compsns. for protection of skin.(I) may also be used for diagnostic purposes. Admin. is oral, topical or parenteral.
Dwg.0/4
FS CPI
FA AB; DCN
MC CPI: **B03-G**; B12-K04A; B14-C03; B14-G01; B14-G02C; B14-H01A; B14-H01B; B14-N01; B14-N17; B14-R01; **B14-S04**; D08-B09A; E07-A03B; E10-E04C; E10-E04F

L146 ANSWER 8 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-167343 [20] WPIX
DNC C1994-076677
TI **Vitamin-d** analogues with antiinflammatory and immunomodulatory activity - used to treat e.g. hyperdarathyroidism, **diabetes** mellitus, hypertension, acne, alopecia, skin ageing, etc..
DC B05 E15
IN CALVERLEY, M J; PEDERSEN, H
PA (LOVE) LEO PHARM PROD LTD
CYC 47
PI WO 9410139 A1 19940511 (199420)* 50p C07C401-00
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AU BB BG BR BY CA CZ FI HU JP KP KR KZ LK LV MG MN MW NO NZ PL RO RU SD SK UA US UZ VN
AU 9454181 A 19940524 (199434) C07C401-00
FI 9501968 A 19950425 (199529) C07C000-00
EP 667856 A1 19950823 (199538) EN C07C401-00
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
AU 671326 B 19960822 (199642) C07C401-00
JP 08503700 W 19960423 (199645) 48p C07C401-00
NZ 257533 A 19970624 (199732) C07C401-00
EP 667856 B1 19980204 (199810) EN 28p C07C401-00
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
US 5710142 A 19980120 (199810) 22p A61K031-59
DE 69316910 E 19980312 (199816) C07C401-00
ES 2114619 T3 19980601 (199829) C07C401-00
RU 2128168 C1 19990327 (200024) C07C401-00
ADT WO 9410139 A1 WO 1993-DK351 19931101; AU 9454181 A WO 1993-DK351 19931101, AU 1994-54181 19931101; FI 9501968 A WO 1993-DK351 19931101, FI 1995-1968 19950425; EP 667856 A1 EP 1993-924535 19931101, WO 1993-DK351 19931101; AU 671326 B AU 1994-54181 19931101; JP 08503700 W WO 1993-DK351 19931101, JP 1994-510578 19931101; NZ 257533 A NZ 1993-257533 19931101, WO 1993-DK351

19931101; EP 667856 B1 EP 1993-924535 19931101, WO 1993-DK351 19931101; US 5710142 A WO 1993-DK351 19931101, US 1995-428187 19950502; DE 69316910 E DE 1993-616910 19931101, EP 1993-924535 19931101, WO 1993-DK351 19931101; ES 2114619 T3 EP 1993-924535 19931101; RU 2128168 C1 RU 1995-113157 19931101

FDT AU 9454181 A Based on WO 9410139; EP 667856 A1 Based on WO 9410139; AU 671326 B Previous Publ. AU 9454181, Based on WO 9410139; JP 08503700 W Based on WO 9410139; NZ 257533 A Based on WO 9410139; EP 667856 B1 Based on WO 9410139; US 5710142 A Based on WO 9410139; DE 69316910 E Based on EP 667856, Based on WO 9410139; ES 2114619 T3 Based on EP 667856

PRAI GB 1992-23061 19921104

REP 02Jnl.Ref; EP 441467; EP 450743; WO 9115475

IC ICM A61K031-59; C07C000-00; C07C401-00
ICS A61K031-59

AB WO 9410139 A UPAB: 19940705
Vitamin D analogues of formula (I) and their derivs. in which one or more OH gps. are masked as gps. which can be reconverted to OH gps. in vivo. Where squares indicate opt. modified carbon; U, substituting the 24-methylene of 1alpha,25-dihydroxy-20-espi-**vitamin D3**, stands for (CH2)n-Y-(CH2)m n = 0-2; m = 1-2; Y = O or S; R1 = CH2 or ethyl.

The derivs. where the 22-methylene or 23-methylene are replaced by O or both are replaced by CH=CH are also new. One or more C may be substd. with one or more F.

USE - (I) show antiinflammatory and immunomodulatory effects as well as strong activity in inducing differentiation and inhibitory undesirable proliferation of certain cells, including cancer cells and skin cells. Used to treat hyperparathyroidism partic. sec. hyperparathyroidism associated with renal failure, of number of disease states including **diabetes** mellitus, hypertension, acne, alopecia, skin ageing, imbalance in the immune system, of inflammatory diseases such as rheumatoid arthritis and asthma, of diseases characterised by abnormal cell differentiation and/or cell proliferation such as e.g. psoriasis and cancer, for prevention and/or treatment of steroid induced skin atrophy and for promoting osteogenesis and treating osteoporosis.
Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: **B03-G**; B14-C03; B14-G01; B14-H01B; B14-N17; E10-E04F

ABEQ EP 667856 B UPAB: 19980309
Vitamin D analogues of formula (I) and their derivs. in which one or more OH gps. are masked as gps. which can be reconverted to OH gps. in vivo. Where squares indicate opt. modified carbon; U, substituting the 24-methylene of 1alpha,25-dihydroxy-20-espi-**vitamin D3**, stands for (CH2)n-Y-(CH2)m n = 0-2; m = 1-2; Y = O or S; R1 = CH2 or ethyl.

The derivs. where the 22-methylene or 23-methylene are replaced by O or both are replaced by CH=CH are also new. One or more C may be substd. with one or more F.

USE - (I) show antiinflammatory and immunomodulatory effects as well as strong activity in inducing differentiation and inhibitory undesirable proliferation of certain cells, including cancer cells and skin cells. Used to treat hyperparathyroidism partic. sec. hyperparathyroidism associated with renal failure, of number of disease states including **diabetes** mellitus, hypertension, acne, alopecia, skin ageing, imbalance in the immune system, of inflammatory diseases such as rheumatoid arthritis and asthma, of diseases characterised by abnormal cell differentiation and/or cell proliferation such as e.g. psoriasis and cancer, for prevention and/or treatment of steroid induced skin atrophy and for promoting osteogenesis and treating osteoporosis.
Dwg.0/0

ABEQ US 5710142 A UPAB: 19980309
Vitamin D analogues of formula (I) and their derivs. in which one or more OH gps. are masked as gps. which can be reconverted to OH gps. in vivo. Where squares indicate opt. modified carbon; U, substituting the 24-methylene of 1alpha,25-dihydroxy-20-espi-

vitamin D3, stands for (CH2)n-Y-(CH2)m n = 0-2; m = 1-2; Y = O or S; R1 = CH2 or ethyl.

The derivs. where the 22-methylene or 23-methylene are replaced by O or both are replaced by CH=CH are also new. One or more C may be substd. with one or more F.

USE - (I) show antiinflammatory and immunomodulatory effects as well as strong activity in inducing differentiation and inhibitory undesirable proliferation of certain cells, including cancer cells and skin cells. Used to treat hyperparathyroidism partic. sec. hyperparathyroidism associated with renal failure, of number of disease states including **diabetes** mellitus, hypertension, acne, alopecia, skin ageing, imbalance in the immune system, of inflammatory diseases such as rheumatoid arthritis and asthma, of diseases characterised by abnormal cell differentiation and/or cell proliferation such as e.g. psoriasis and cancer, for prevention and/or treatment of steroid induced skin atrophy and for promoting osteogenesis and treating osteoporosis.
Dwg.0/0

L146 ANSWER 9 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-119660 [15] WPIX
CR 1994-135468 [16]
DNC C1994-055385
TI New 25-carboxylic acid cpds., exhibiting **vitamin-D**, anti-proliferative and cell-differentiating activity - are useful for treatment of e.g., psoriasis, acne, malignant tumours and immune disorders e.g. **diabetes**.
DC B01 B05
IN HABEREY, M; KIRSCH, G; NEEF, G; SCHWARZ, K; STEINMEYER, A; THIEROFF-EKERDT, R; WIESINGER, H; THIEROFF, E R; THIEROFFEKERDT, R
PA (SCHD) SCHERING AG
CYC 28

PI	DE 4234382	A1	19940407 (199415)*	17p	C07C401-00
	AU 9351771	A	19940426 (199432)		C07C401-00
	ZA 9307421	A	19940727 (199432)	154p	C07C000-00
	FI 9501614	A	19950405 (199527)		C07C000-00
	NO 9501318	A	19950602 (199532)		C07C401-00
	EP 663902	A1	19950726 (199534) DE		C07C401-00
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE				
	CN 1094034	A	19941026 (199542)		C07C401-00
	CZ 9500873	A3	19951018 (199549)		C07C401-00
	TW 268938	A	19960121 (199615)		C07C401-00
	US 5583125	A	19961210 (199704)	36p	C07C401-00
	IL 107185	A	19980222 (199814)		C07C401-00
	SK 280651	B6	20000516 (200036)		C07C401-00
	MX 189547	B	19980806 (200037)		C07C401-000
	NO 309599	B1	20010226 (200115)		C07C401-00

ADT DE 4234382 A1 DE 1992-4234382 19921006; AU 9351771 A AU 1993-51771 19931006; ZA 9307421 A ZA 1993-7421 19931006; FI 9501614 A FI 1995-1614 19950405; NO 9501318 A WO 1993-EP2814 19931006, NO 1995-1318 19950405; EP 663902 A1 EP 1993-922944 19931006, WO 1993-EP2814 19931006; CN 1094034 A CN 1993-114425 19931006; CZ 9500873 A3 CZ 1995-873 19931006; TW 268938 A TW 1993-109359 19931108; US 5583125 A US 1993-132176 19931006; IL 107185 A IL 1993-107185 19931005; SK 280651 B6 WO 1993-EP2814 19931006, SK 1995-458 19931006; MX 189547 B MX 1993-6204 19931006; NO 309599 B1 WO 1993-EP2814 19931006, NO 1995-1318 19950405
FDT AU 9351771 A Based on WO 9407853; EP 663902 A1 Based on WO 9407853; SK 280651 B6 Previous Publ. SK 9500458; NO 309599 B1 Previous Publ. NO 9501318
PRAI DE 1992-4234382 19921006; DE 1993-4317415 19930518
REP 01Jnl.Ref; EP 421561; WO 9100271; WO 9309093
IC ICM C07C000-00; C07C401-00; C07C401-000
ICS A61K031-059; A61K031-575; A61K031-59
AB DE 4234382 A UPAB: 20010317
25-Carboxylic acid cpds. of formula (I) are new. In (I), R1, R3 and R24 = H, 1-9C alkanoyl or aroyl; -OH = an alpha- or beta-hydroxy gp.; both R4, R41 = H, Cl, F, CF3 or opt. unsatd. 1-4C hydrocarbyl; or CR4R41 = a 3-7

membered, opt. unsatd. carboxylic; Y = CONR5R51, COOR6, or CN; R5, R51 = H or 1-8C alkyl; R6 = H, 1-8C alkyl, an unsatd. 3-8C hydrocarbyl gp., or a gp. of formula (i); m = 0 or 1; n = 2-6, or may also be 1 when m is 1.

Also new are the corresp. cpds. (II), which are as cpds. (I) in which R1 and R3 are hydroxy protecting gps. and Y is as above or may also be a 2-(trimethylsilyl)ethylcarboxylic acid ester (see 'Preparation').

USE/ADVANTAGE - (I) have **vitamin D** activity and can be used in treatment of, e.g., psoriasis, acne, malignant tumours and immune disorders (such as autoimmune disorders including **diabetes** and transplant rejection). (I) also have anti-proliferative and cell-differentiating activity. Admin. is, e.g. oral, topical or parenteral. Dosage is esp. 0.1-1000 (most esp. 1.0-500) micro-g per day.

Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: **B03-G**; B14-G02C; B14-G02D; B14-H01; B14-N17C; B14-N17D; **B14-S04**
ABEQ US 5583125 A UPAB: 19970122

25-Carboxylic acid cpds. of formula (I) are new. R1 and R3 = H, 1-9C satd. alkanoyl or aroyl; R19 and R19a = H or together form an exocyclic methylene gp.; A + B = keto oxygen atom or A = OR24 and B = H, or A = H and B = OR24; R24 = H, 1-9C satd. alkanoyl or aroyl; R21 and R21a = H, Cl or F, 1-4C alkyl; or R21 + R21a = methylene group; or together with carbon atom 20 are a 3-7 membered, opt. unsaturated carbocyclic ring; R4 and R4a = simultaneously H, Cl or F, trifluoromethyl, 1-4C opt. unsaturated hydrocarbon; or R4 and R4a together with carbon atom 25 are a 3 to 7 membered, opt. unsaturated carboxylic ring; Y = C(O)NR5R5', C(O)OR6, C(O)SR6 or CN; R5 and R5' = H or 1-8C alkyl; R6 = e.g. H, 1-8C alkyl or 3-8C unsaturated hydrocarbon; m = 0 or 1; and n = 2-6; and if m = 1, n can also be 1.

Dwg.0/0

L146 ANSWER 10 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-034947 [04] WPIX
DNC C1994-016119
TI **Vitamin-D** analogues with antiinflammatory and immunomodulatory activity - used to treat e.g. hyperparathyroidism, auto-immune disease e.g. **diabetes** mellitus, hypertension, acne, alopecia, skin ageing, etc..
DC B01 B05
IN BRETTING, C A S; BRETTING, C A; BRETTING, C
PA (LOVE) LEO PHARM PROD LTD; (LOVE) LOEVENS KEMISKE FAB PROD AS
CYC 43
PI WO 9401398 A1 19940120 (199404)* EN 53p C07C401-00
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AU BB BG BR CA CZ FI HU JP KP KR LK MG MN MW NO NZ PL RO RU SD SK UA US VN
AU 9343111 A 19940131 (199422) C07C401-00
FI 9500023 A 19950102 (199513) C07C000-00
EP 648207 A1 19950419 (199520) EN C07C401-00
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
HU 68025 T 19950529 (199528) C07C401-00
AU 667378 B 19960321 (199619) C07C401-00
US 5545633 A 19960813 (199638) 16p A61K031-59
JP 08504746 W 19960521 (199646) 49p C07C401-00
EP 648207 B1 19970312 (199715) EN 33p C07C401-00
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69308852 E 19970417 (199721) C07C401-00
ES 2101319 T3 19970701 (199736) C07C401-00
RU 2114825 C1 19980710 (200001)
FI 106120 B1 20001130 (200067) C07C401-00
ADT WO 9401398 A1 WO 1993-DK196 19930607; AU 9343111 A AU 1993-43111 19930607; FI 9500023 A WO 1993-DK196 19930607, FI 1995-23 19950102; EP 648207 A1 EP 1993-912681 19930607, WO 1993-DK196 19930607; HU 68025 T WO 1993-DK196 19930607, HU 1994-2484 19930607; AU 667378 B AU 1993-43111 19930607; US 5545633 A WO 1993-DK196 19930607, US 1994-295755 19940901; JP 08504746 W

WO 1993-DK196 19930607, JP 1994-502829 19930607; EP 648207 B1 EP 1993-912681 19930607, WO 1993-DK196 19930607; DE 69308852 E DE 1993-608852 19930607, EP 1993-912681 19930607, WO 1993-DK196 19930607; ES 2101319 T3 EP 1993-912681 19930607; RU 2114825 C1 RU 1994-46411 19930607; FI 106120 B1 WO 1993-DK196 19930607, FI 1995-23 19950102

FDT AU 9343111 A Based on WO 9401398; EP 648207 A1 Based on WO 9401398; HU 68025 T Based on WO 9401398; AU 667378 B Previous Publ. AU 9343111, Based on WO 9401398; US 5545633 A Based on WO 9401398; JP 08504746 W Based on WO 9401398; EP 648207 B1 Based on WO 9401398; DE 69308852 E Based on EP 648207, Based on WO 9401398; ES 2101319 T3 Based on EP 648207; FI 106120 B1 Previous Publ. FI 9500023

PRAI GB 1992-14202 19920703

REP 01Jnl.Ref; WO 9203414

IC ICM A61K031-59; C07C000-00; C07C401-00
ICS A61K031-59

AB WO 9401398 A UPAB: 19940608

Vitamin D analogues of formula (I) and their prodrugs in which one or more of the hydroxy gps. mashed as gps. which can be converted to hydroxy gps. in vivo are new. X = H or hydroxy; R1, R2 = H or 1-6C hydrocarbyl; or CR1R2 = a 3-8C carbocyclic ring; Q = single bond or 108C hydrocarbylene diradical, where hydrocarbyl diradical indicates the residue after removal of 1 and 2 H atoms from a straight, branched or cyclic opt. substd. hydrocarbyl and R1,R2 or Q may be opt. substd. with 1 or more deuterium or F atoms.

USE/ADVANTAGE - (I) show antiinflammatory and immunomodulating activity and strong activity in inducing differentiation and inducing undesirable proliferation of cells, e.g. cancer cells. (I) may be used to treat hyperparathyroidism, and autoimmune diseases including **diabetes** mellitus, hypertension, acne, alopecia, skin ageing (including photoageing), imbalance in the immune system, inflammatory diseases e.g. rheumatoid arthritis and asthma, diseases characterised by abnormal cell differentiation and/or cell proliferation e.g. psoriasis. steroid induced skin atrophy and for promoting osteogenesis and treating osteoporosis. (I) show more potent effects on cell proliferation/differentiation, greater selectivity in favour of potents effects on cell differentiation and proliferation against the effects of Ca metabolism, more potent effects on prodn. and action of interleukins and greater selectivity in favour of the effects on interleukin prodn. and action against the effects on Ca metabolism. (I) are partic. suited for local and systemic treatment and prophylaxis. (I) are suitable for combination with other drugs.

In formulations, the active ingredient comprises 0.1ppm to 0.1% by wt. of the formulation. For systemic disorders, dosage is 0.1-100 (0.2-25) mg/day). For topical treatment of dermatological disorders 0.1-500 (0.1-100) mg are administered for topical treatment in ophthalmology, drops or gels contg. 0.1-500 (0.1-100)m of (I) are administered oral dosage is 0.05-50 (0.1-25)mg dosage unit.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: **B03-G**; B14-C03; B14-G02D; B14-G03; B14-H01; B14-K01A; B14-N01

ABEQ US 5545633 A UPAB: 19960924

A compound of the formula (I)

wherein X is hydrogen or hydroxy; R1 and R2 which may be the same or different, stand for hydrogen or a C1-C6 hydrocarbyl radical optionally substituted with one or more deuterium or fluorine atoms; or R1 and R2, taken together with the carbon atom (starred in formula I) bearing the group X, can form a C3-C8 carbocyclic ring; Q is a single bond or a C1-C8 hydrocarbylene diradical optionally substituted with one or more deuterium or fluorine atoms; or a prodrug of I in which one or more of the hydroxy groups are masked as groups which can be reconverted to hydroxy groups in vivo.

Dwg.0/0

ABEQ EP 648207 B UPAB: 19970410

A compound of the formula (I) in which formula X is hydrogen or hydroxy;

R1 and R2, which may be the same or different, stand for hydrogen or a C1-C6 hydrocarbyl radical; or R1 and R2, taken together with the carbon atom (starred in formula 1) bearing the group X, can form a C3-C8 carbocyclic ring; Q is a single bond or a C1-C8 hydrocarbylene diradical, the expression hydrocarbyl radical (hydrocarbylene diradical) indicating the residue after removal of 1 (2) hydrogen atom(s) from a straight, branched or cyclic saturated or unsaturated hydrocarbon; R1, R2 and/or Q may be optionally substituted with one or more deuterium or fluorine atoms; and prodrugs of 1 in which one or more of the hydroxy groups are masked as groups which can be reconverted to hydroxy groups IN VIVO. Dwg.0/0

L146 ANSWER 11 OF 11 WPIX COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1991-222823 [30] WPIX
DNC C1991-096772
TI New immuno modulating **vitamin-D** analogues - used for treating auto immune diseases including **diabetes** mellitus, hypertension, skin ageing, inflammatory diseases and cancer.
DC B05 D21 E14
IN HANSEN, K
PA (LOVE) LEO PHARM PROD LTD; (LOVE) LOEVENS KEMISKE FAB PROD AS
CYC 34
PI WO 9109841 A 19910711 (199130)*
RW: AT BE CH DE DK ES FR GB GR IT LU NL SE
W: AU BB BG BR CA FI HU JP KP KR LK MC MG MW NO RO SD SU US
AU 9170662 A 19910724 (199143)
FI 9202815 A 19920617 (199239) C07C000-00
EP 506794 A1 19921007 (199241) EN 30p C07C401-00
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
JP 05502875 W 19930520 (199325) 15p C07C401-00
EP 506794 B1 19940824 (199433) EN 34p C07C401-00
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69011872 E 19940929 (199438) C07C401-00
ES 2062758 T3 19941216 (199505) C07C401-00
US 5387582 A 19950207 (199512) 11p C07C401-00
IE 64534 B 19950809 (199539) C07C401-00
FI 95241 B 19950929 (199544) C07C401-00
ADT FI 9202815 A WO 1990-DK323 19901210, FI 1992-2815 19920617; EP 506794 A1 WO 1990-DK323 19901210, EP 1991-901716 19901210; JP 05502875 W WO 1990-DK323 19901210, JP 1991-502200 19901210; EP 506794 B1 WO 1990-DK323 19901210, EP 1991-901716 19901210; DE 69011872 E DE 1990-611872 19901210, WO 1990-DK323 19901210, EP 1991-901716 19901210; ES 2062758 T3 EP 1991-901716 19901210; US 5387582 A WO 1990-DK323 19901210, US 1992-838795 19920317; IE 64534 B IE 1990-4446 19901210; FI 95241 B WO 1990-DK323 19901210, FI 1992-2815 19920617
FDT EP 506794 A1 Based on WO 9109841; JP 05502875 W Based on WO 9109841; EP 506794 B1 Based on WO 9109841; DE 69011872 E Based on EP 506794, Based on WO 9109841; ES 2062758 T3 Based on EP 506794; US 5387582 A Based on WO 9109841; FI 95241 B Previous Publ. FI 9202815
PRAI GB 1989-29059 19891222
REP EP 184119; EP 184112
IC ICM C07C401-00
ICS A61K031-59
AB WO 9109841 A UPAB: 19930928
Vitamin D analogues of formula (I) and their derivs. in which at least 1 OH is transformed into -O-acyl or -O-glycosyl or phosphate ester gp. which are hydrolysable in vivo are new. R1, R2 = H, 1-5C alkyl or 3-7C cycloalkyl, or together with the C star atom forms a 3-8C carbocyclic ring. X = H or OH. R3, R4 = H, 1-5C alkyl or halo. n = 0, 1 or 2. m = 0, 1 or 2. 2 cpds. are specifically claimed, e.g. 1(S),3(R)-dihydroxy-20(R)-(3-(2-hydroxy-2-propyl) -phenylmethoxy)-9,10-seco-pregna-5(Z), 7(E), 10(19)-triene. Prepn. of (I) comprises alkylating 1(S), 3(R)-bis-(t-butyl dimethylsilyloxy) -9,10-seco-pregna-5(E), 7(E), 10(19)-triene 20(R)-ol under basic conditions and subjecting the prod. to triplet sensitised photoisomerisation. A unit dose contains 0.1-50 (0.2-25) microg of (I).

USE/ADVANTAGE - For treating autoimmune diseases, including **diabetes** mellitus, hypertension, skin ageing, inflammatory disease such as rheumatoid arthritis and asthma and diseases characterised by abnormal cell differentiation and/or cell proliferation, and/or imbalance in the immune system (claimed). (I) promote the differentiation of hair follicle cells and are also used for treating alopecia. (I) have good receptor binding selectivity, good bioavailability and good chemical and metabolic stability. (I) are also used for treating cancer. @(30pp Dwg.No.0/0)@

FS CPI

FA AB; DCN

MC CPI: **B03-G**; B12-A01; B12-A06; B12-A07; B12-D02; B12-D03; B12-D07; B12-F05; B12-G04A; B12-G05; B12-G07; **B12-H05**; B12-K02; D09-E; E10-E04C

ABEQ EP 506794 A UPAB: 19930928

Vitamin D analogues of formula (I) and their derivs. in which at least 1 OH is transformed into -O-acyl or -O-glycosyl or phosphate ester gp. which are hydrolysable in vivo are new. R1, R2 = H, 1-5C alkyl or 3-7C cycloalkyl, or together with the C star atom forms a 3-8C carbocyclic ring. X = H or OH. R3, R4 = H, 1-5C alkyl or halo, n = 0, 1 or 2. m = 0, 1 or 2. 2 cpds. are specifically claimed, e.g, 1(S),3(R)-dihydroxy-20(R)- (3-(2-hydroxy-2-propyl) -phenylmethoxy)-9,10-seco-pregna-5(Z), 7(E), 10(19)-triene. Prepn. of (I) comprises alkylating 1(S), 3(R)-bis-(t-butyl dimethylsilyloxy) -9,10-seco-pregna-5(E), 7(E), 10(19)-triene 20(R)-ol under basic conditions and subjecting the prod. to triplet sensitised photoisomerisation. A unit dose contains 0.1-50 (0.2-25) micro-g of (I).

USE/ADVANTAGE - For reacting autoimmune diseases, including **diabetes** mellitus, hypertension, skin ageing, inflammatory disease such as rheumatoid arthritis and asthma and diseases characterised by abnormal cell differentiation and/or cell proliferation, and/or imbalance in the immune system (claimed). (I) promote the differentiation of hair follicle cells and are also used for treating alopecia. (I) have good receptor binding selectivity, good bioavailability and good chemical and metabolic stability. (I) are also for treating cancer.

ABEQ JP 05502875 W UPAB: 19931116

Vitamin D analogues of formula (I) and their derivs. in which at least 1 OH is transformed into -O-acyl or -O-glycosyl or phosphate ester gp. which are hydrolysable in vivo are new. R1, R2 = H, 1-5C alkyl or 3-7C cycloalkyl, or together with the C star atom forms a 3-8C carbocyclic ring. X = H or OH, R3, R4 = H, 1-5C alkyl or halo; n = 0, 1 or 2; m = 0, 1 or 2; 2 cpds. are specifically claimed, e.g. 1(S), 3(R)-dihyroxy-20(R)- (3-(2-hydroxy-2-propyl). -phenylmethoxy) -9,10-seco-pregna-5(Z), 7(E), 10(19)-triene.

Prepn. of (I) comprises alkylating 1(S), 3(R)-bis-(t-butyl dimethylsilyloxy)-9,10-seco-pregna-5(E), 7(E), 10(19)-triene 20(R)-ol under basic conditions and subjecting the prod. to triplet sensitised photoisomerisation. A unit dose contains 0.1-50 (0.2-25) micro-g of (I).

USE/ADVANTAGE - For treating autoimmune diseases, including **diabetes** mellitus, hypertension, skin ageing, inflammatory disease such as rheumatoid arthritis and asthma and diseases characterised by abnormal cell differentiation and/or cell proliferation, and/or imbalance in the immune system. (I) promote the differentiation of hair follicle cells and are also used for treating alopecia. (I) have good receptor binding selectively, good bioavailability and good chemical and metabolic stability. (I) are also used for treating cancer.

ABEQ EP 506794 B UPAB: 19941010

A compound of the formula I in which R1 and R2 may be the same or different and stand for hydrogen, C1-C5-alkyl, C3-C7-cycloalkyl, or taken together with the carbon atom (starred in formula I), bearing the groups X, R1 and R2, can form a C3-C8 carbocyclic ring; X stands for hydrogen or hydroxy, R3 and R4, which may be the same or different stand for hydrogen, C1-C5-alkyl or halogen, n is 0, 1 or 2 and m is 0, 1 or 2; and derivatives of the compounds of formula I in which one or more hydroxy groups have been transformed into -O-acyl or-O-glycosyl or phosphate ester groups, such masked groups being hydrolysable in vivo.

Dwg.0/34
ABEQ US 5387582 A UPAB: 19950328
Vitamin D analogue of formula (I) and their derivs.
and diastereoisomers are new.
R1,R2 H, 1-3C alkyl, 3-7C cycloalkyl, or together form 3-8C carbocyclic ring; X = H or OH; R3,R4 = H, 1-5C alkyl or halo; n = 0-2; m = 0-2.
Derivs. have one or more OH gps. transformed to -O-acyl or -O-glycosyl or in vivo-hydrolysable phosphate ester gps.
Prodn. comprises alkylating 1(S),3(R)-bis(tert-butyldimethylsilyloxy)-9,10-seco-pregna--5(E),7(E),10(19)-triene-20(R)-ol under basic conditions with a side chain building block of formula (III), then photoisomerising under triplet-sensitised conditions, and deprotection.
Z = leaving gp.; R = (a); Y = H or OH opt. protected.
Specifically claimed cpds. are 1(S),3(R)-dihydroxy-20(R)-(3-(2-hydroxy-2-propyl)-phenylmethoxy)-9,10- seco-pregna--5(Z),7(E),10(19)-triene and 1(S),3(R)-dihydroxy-20(R)- (3-(3-hydroxy-3-phenyl)-phenylmethoxy-9,10-seco-pregna-5(Z),7(E),10(19)-triene.
USE - Effective immunomodulators which also inhibit cellular proliferation of cancer and skin cells, used to treat autoimmune diseases, **diabetes**, hypertension, inflammation, rheumatoid arthritis, and asthma, and abnormal cell, differentiation and proliferation. Unit dosage is 0.1-50 mcg.
Dwg.0/0

=> d his

(FILE 'HOME' ENTERED AT 12:39:03 ON 16 SEP 2001)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 12:39:20 ON 16 SEP 2001
E DELUCA H/AU
L1 1095 S E3,E6,E7,E9,E10
E MCCARY L/AU
L2 4 S E4,E5
E MC CARY L/AU
E ZELLA J/AU

FILE 'REGISTRY' ENTERED AT 12:41:53 ON 16 SEP 2001
L3 1 S 1406-16-2

FILE 'HCAPLUS' ENTERED AT 12:41:58 ON 16 SEP 2001
L4 6051 S L3
L5 253 S L1,L2 AND L4
L6 845 S L1,L2 AND VITAMIN(L)D#
L7 94 S L1,L2 AND VITAMIN(L)D2
L8 548 S L1,L2 AND VITAMIN(L)D3
L9 16799 S VITAMIN D
L10 2247 S 1 ALPHA 25 DIHYDROXYVITAMIN D3
L11 52 S 1 ALPHA HYDROXY VITAMIN D3
L12 630 S 1 ALPHA HYDROXYVITAMIN D3
L13 65 S 1()ALPHA()(HYDROXYVITAMIN OR HYDROXY VITAMIN)()D2
L14 0 S 19 NOR 1 25 DIHYDROXY 21 EPI VITAMIN D3
L15 0 S 19 NOR 1 25 DIHYDROXY 21 EPIVITAMIN D3
L16 1 S 19(L)NOR(L)DIHYDROXY(L)(EPIVITAMIN OR EPI(L)VITAMIN)(L)D3
L17 0 S 1 25 DIHYDROXY (L) DEHYDRO (L) 24 (L) HOMOVITAMIN(L)D3
L18 0 S 1 25 DIHYDROXY (L) DEHYDRO (L) 24 (L) HOMO (L) VITAMIN(L)D3
L19 1 S DIHYDROXY (L) DEHYDRO (L) HOMO (L) VITAMIN(L)D3
L20 3079 S 1 25 OH 2D3
L21 0 S 19 NOR 1 25 OH 2D3
L22 0 S 22E 1 25 OH 2D3
L23 1 S 1 25 OH 2 24 HOMO D3

FILE 'REGISTRY' ENTERED AT 12:52:50 ON 16 SEP 2001
L24 3 S 32222-06-3 OR 41294-56-8 OR 54573-75-0

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     FILE 'HCAPLUS' ENTERED AT 12:53:30 ON 16 SEP 2001
L25         9243 S L24
L26          341 S L1,L2 AND L25
L27          911 S L5-L8,L26
L28          201 S L1,L2 AND L10-L23
L29          915 S L27,L28

     FILE 'REGISTRY' ENTERED AT 12:54:27 ON 16 SEP 2001

     FILE 'HCAPLUS' ENTERED AT 12:54:35 ON 16 SEP 2001
                 SET SMARTSELECT ON
L30           SEL L29 1- RN :    2009 TERMS
                 SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 12:55:00 ON 16 SEP 2001
L31         2001 S L30
L32              STR
L33           50 S L32 CSS
L34         2873 S L32 CSS FUL
                 SAV L34 KARL769/A
L35          325 S L34 AND L31
L36         2874 S L3,L24,L35,L34
L37            2 S GLUCOSE/CN
L38            1 S INSULIN/CN

     FILE 'HCAPLUS' ENTERED AT 13:06:11 ON 16 SEP 2001
L39        15848 S L36
                 E DIABET/CW
L40        43215 S E4,E5
                 E ANTIDIABET/CW
L41         8717 S E4,E5
                 E DIBIABET/CT
                 E DIABET/CT
                 E E4+ALL
L42         1984 S E1
                 E E2+ALL
L43         1149 S E2+NT
                 E DIBIABET/CT
                 E DIABET/CT
                 E E4+ALL
                 E E3+ALL
L44        39552 S E4+NT
                 E E11+ALL
L45         4246 S E2,E3
                 E E16+ALL
L46         5435 S E2
L47          176 S L39 AND L40-L46
L48          165 S L39 AND L37
L49          202 S L39 AND L38
L50          449 S L47-L49
                 E BLOOD GLUCOSE/CT
                 E E3+ALL
L51        10188 S E1
L52         7915 S E2
L53           20 S L39 AND L51,L52
                 E INSULIN/CT
                 E E3+ALL
L54         9092 S E6,E8-E10
L55        11935 S E14
L56         4309 S E13+NT
L57           24 S L39 AND L54-L56
L58          460 S L50,L53,L57
L59           93 S L36 (L) THU/RL AND L58
L60            4 S L1,L2 AND L58
                 E PANCREATIC ISLET/CT
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                E E21+ALL
L61          57 S L39 AND E11,E12,E10+NT
L62          52 S L39 AND E9
L63         518 S L58,L61,L62
L64           6 S L1,L2 AND L63
L65         102 S L36 (L) THU/RL AND L63
L66         102 S L59,L65
L67          33 S L66 AND ?DIABET?(L)MELLITUS
L68           6 S L66 AND ?DIABET?(L) TYPE I
L69           3 S L66 AND ?DIABET?(L) TYPE 1
L70          17 S L66 AND ?DIABET?(L) ?INSULIN?
L71          37 S L67-L70
L72       11100 S L34
L73          54 S L72 AND L66
L74          27 S L73 AND L71
L75          25 S L74 NOT UPDATE/TI
L76          27 S L73 NOT L74
L77          11 S L76 AND (ANALOG# OR DIABET? OR RXR OR ISLET OR UREMI#)/TI
L78           8 S L77 NOT (RETINOID OR BREAST OR HYPERCALCEMIA)/TI
L79          39 S L64,L75,L78
L80          17 S L24 AND L79
L81          39 S L79,L80

     FILE 'REGISTRY' ENTERED AT 13:27:32 ON 16 SEP 2001

     FILE 'HCAPLUS' ENTERED AT 13:27:47 ON 16 SEP 2001
L82         722 S L1,L2 AND L39
L83          27 S L82 NOT L29
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 13:31:39 ON 16 SEP 2001
L84          22 S E1-E22
L85          22 S L84 NOT L3,L24
L86         322 S L35 NOT L3,L24
L87         332 S L84,L86
L88          75 S L87 AND NOR
L89           9 S L87 AND HOMO
L90           6 S L87 AND EPI
L91           7 S L89 AND D3
L92          75 S 19 AND L88
L93           2 S L92 AND D2
L94           4 S L3,L24

     FILE 'REGISTRY' ENTERED AT 13:38:32 ON 16 SEP 2001

     FILE 'MEDLINE' ENTERED AT 13:38:45 ON 16 SEP 2001
L95       17088 S L36
L96         600 S L95 AND (L37 OR L38 OR GLUCOSE OR INSULIN)
                E DIABETES/CT
                E E80+ALL
L97      143248 S E6+NT
L98        1261 S E32+NT
L99        1859 S E34+NT
L100        186 S L95 AND L97-L99
                E VITAMIN D/CT
                E E3+ALL
L101      22798 S E4+NT
L102        232 S L101 AND L97-L99
L103        232 S L100,L102
L104         59 S L103 NOT AB/FA
L105        126 S L101/MAJ AND L103
L106         48 S ((VITAMIN D+NT)(L)(TU OR PD OR AD))/CT AND L105
L107     112117 S L97/MAJ OR L98/MAJ OR L99/MAJ
L108         34 S L107 AND L106
                SEL DN L108 1 5 8 9 10 14 15 17 18 20 31
L109         11 S E1-E22
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L110          14 S L106 NOT L108
                 SEL DN L110 7 8
L111           2 S E23-E26
L112         168 S L107 AND L103
L113         134 S L112 NOT L106,L108
                 SEL DN 48 L113
L114           1 S E27-E28
L115          14 S L109,L111,L114 AND L95-L114

     FILE 'MEDLINE' ENTERED AT 13:56:48 ON 16 SEP 2001

     FILE 'WPIX' ENTERED AT 13:57:16 ON 16 SEP 2001
L116         486 S ?CALCIFEROL?
L117        1987 S VITAMIN () (D OR D2 OR D3 OR D4)
L118        1854 S V340/M0,M1,M2,M3,M4,M5,M6
L119        1392 S (B03-G OR C03-G)/MC
L120        3002 S L116-L119
                 E VITAMIN D/DCN
                 E E4+ALL
L121          73 S E2
L122         528 S E4 OR 0007/DRN
L123         657 S E6 OR 0276/DRN
L124          53 S E8
L125          16 S E10
L126           3 S E12
L127          61 S E14
L128          20 S E16
L129           5 S E18
L130          92 S E20 OR 2013/DRN
L131          39 S E22
L132        3126 S L120-L131
L133          51 S L132 AND (B14-S04 OR C14-S04)/MC
L134          27 S L132 AND (B12-H05 OR C12-H05)/MC
L135          98 S L132 AND P816/M0,M1,M2,M3,M4,M5,M6
L136         122 S L132 AND ?DIABET?
L137         141 S L133-L136
L138          27 S L137 AND DIABET?/TI
L139          14 S L138 AND VITAMIN/TI
L140           1 S L138 AND CHOLECALCIFEROL/TI
L141          15 S L139,L140
L142          10 S L141 NOT (RECEPTOR OR CURCUMIN OR RETINOPATHY OR BONE OR CANE
L143         114 S L137 NOT L138-L142
L144          41 S L143 AND L133
L145           1 S L144 AND ENDOCRIN?/TI
L146          11 S L145,L142

     FILE 'WPIX' ENTERED AT 14:09:59 ON 16 SEP 2001
           SET COST ON
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